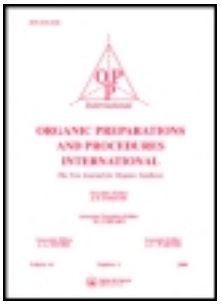

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RECENT DEVELOPMENTS IN HYDANTOIN CHEMISTRY. A REVIEW

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RECENT DEVELOPMENTS IN HYDANTOIN CHEMISTRY. A REVIEW

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INTRODUCTION

Nearly twenty years after the last review on the chemistry of hydantoins published by López and Trigo[1] in 1985, the rapid development of organic medicinal and pharmaceutical chemistry has led to an enhanced interest in hydantoins once again. New synthetic methods have been developed or older ones applied to new technologies or performed under improved conditions. Further, knowledge about the reactivity of hydantoins has increased enormously. Therefore, this review will reflect all new issues concerning the synthesis and reactions of hydantoins, utilizing publications appearing since 1985 and up to May 2004.

1. Biological Effects and Therapeutic Applications of Hydantoins

The discovery of biological activities of hydantoins has made amazing progress during the last two decades, and hydantoin derivatives have been therapeutically applied (*Fig. 1*).

Biological and Pharmacological Effects of Hydantoins

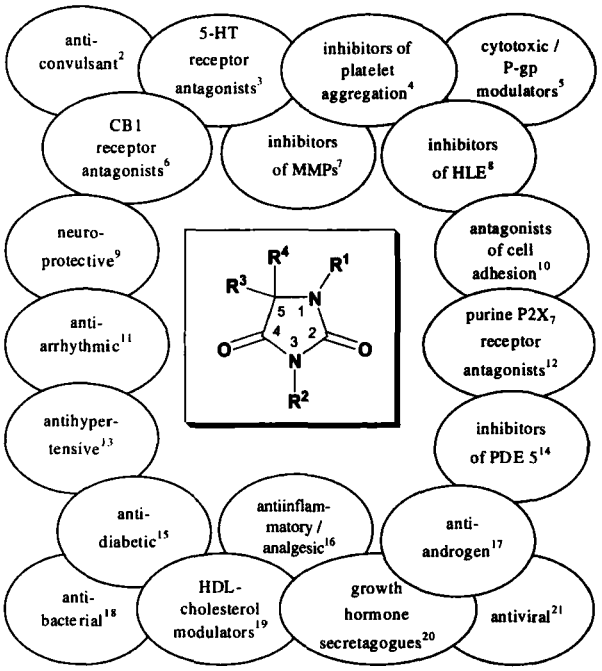


Fig. 1

Beside the traditional usage, *e.g.* of phenytoin as antiepileptic[2h,2i,22], of azimilide as an antiarrhythmic[23], of nitrofurantoin as an antibacterial substance or of dantrium as a sceletal muscle relaxant, hydantoins have also been developed as new drugs in the treatment of other diseases, for example, nilutamide, which was approved by the FDA in 1996 as a nonsteroidal, orally active antiandrogen in the therapy of metastatic prostate cancer (*Fig. 2*).[17b,17c] However, detailed information on pharmacological effects and therapeutic applications of hydantoins will not be part of the present review.

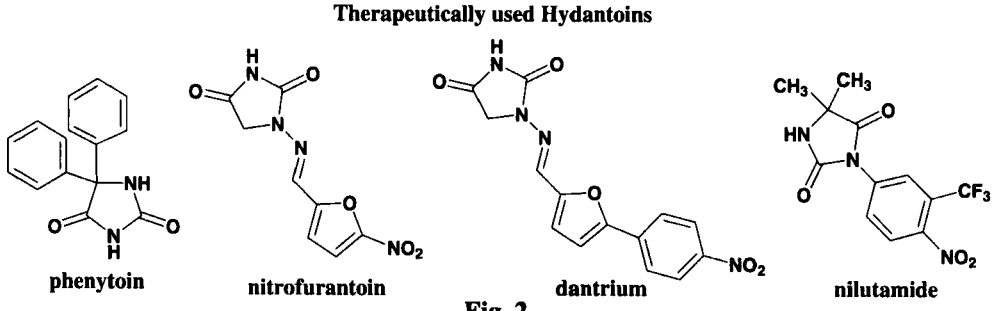


Fig. 2

2. Natural Products Containing a Hydantoin Moiety

Hydantoins and some of their derivatives are structural units frequently encountered in naturally occurring substances, mostly of marine organisms, but also of bacteria. 5-(*p*-Hydroxybenzyl)hydantoin could be isolated from an endophytic fungus from an estuarine mangrove on the South China Sea coast.[24] Examples for many alkaloids extracted from sponges or corals which contain a hydantoin moiety (*Fig. 3*) are the well-known aplysinopsins with cytotoxic properties,[5a,5e,25,26] axinohydantoins from *Axinella*,[5b] *Hymeniacidon*[27] and *Stylotella* species inhibiting

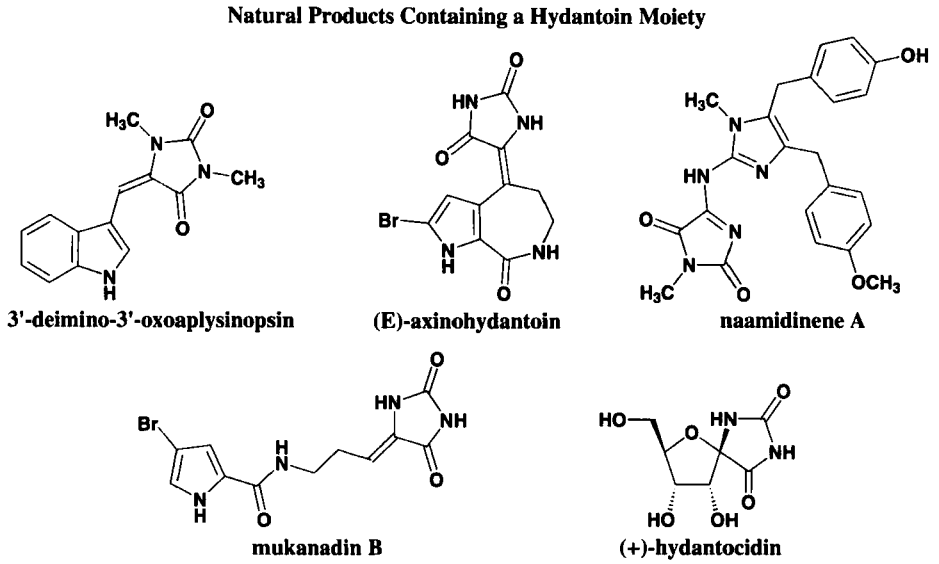


Fig. 3

protein kinase C,[28,29] naamidinene A, a dehydro hydantoin derivative from the genus *Leucetta*,[30] and mukanadin B from *Agelas* species.[31] Hydantocidin is a spiro nucleoside from *Streptomyces hygroscopicus*,[32,33] which possesses herbicidal and plant growth regulatory activity due to the inhibition of adenylsuccinate synthetase.[34]

3. Historical Outline

The history of hydantoins can be dated back to the year 1861 when Adolph von Baeyer,[35] a former Munich professor of organic chemistry and Nobel prize winner in 1905, discovered hydantoin itself. He found that the 2,4-imidazolidinedione is a product of the *hyd*rogenolysis of all*antoin*. Inversion of the biological degradation of uric acid *via* allantoin was accomplished in the laboratories of Grimaux by reacting different ureas with glyoxylic acid.[36] The first classical synthetic pathway to hydantoins was found in 1873 when Friedrich Urech published his work on the formation of 5-monosubstituted hydantoins from amino acids and potassium cyanate followed by cyclization of the intermediate hydantoic acid (ureido acid) with hydrochloric acid.[37] Later, Read prepared 5,5-disubstituted hydantoins from amino nitriles (which were already available from the Strecker and Tiemann syntheses) and potassium cyanate and cyclization of the formed ureido acid with hydrochloric acid.[38] Similar to this approach is the acid-catalyzed cyclization of thioureido acids obtained from reaction of alkyl or aryl isothiocyanates with amino acids[39] or amino nitriles, respectively. Another general access to 5-mono and 5,5-disubstituted hydantoins was provided by the Bucherer-Bergs method,[40] comprising the condensation of carbonyl compounds with potassium cyanide and ammonium carbonate. The condensation of α-dicarbonyl compounds with ureas represented a further classical methodology that involved a step similar to the benzilic acid rearrangement, first applied in the synthesis of phenytoin by Biltz.[41]

I. METHODS OF SYNTHESIS

1. Solution-phase Syntheses

There are several approaches to hydantoins starting from different building blocks. The most important principles of hydantoin construction are shown in *Fig. 4*. Hydantoins can be formed from ureas (highlighted) and carbonyl compounds (*Fig. 4a*). Examples for such preparations including those of the Biltz synthesis are given in chapter I.1.a. According to the Bucherer-Bergs method (chapter I.1.b), N-1 and N-3 unsubstituted hydantoins can be generated by the reaction of a carbonyl compound with inorganic cyanide and introducing a second nitrogen and a carbonyl unit by ammonium carbonate (highlighted, *Fig. 4b*). Furthermore, the Read-type reaction (chapter I.1.c) of amino acids (esters) with inorganic iso(thio)cyanates (highlighted) furnishes hydantoins with an unsubstituted N-3 position (*Fig. 4c*). The use of alkyl or aryl iso(thio)cyanates (highlighted) results in substitution at nitrogen N-3 (*Fig. 4d*). Such examples can be found in chapter I.1.d. Amino amides (*Fig. 4e*) already contain four ring atoms, and an

introduced C-1 unit (highlighted) can complete the hydantoin ring (chapter I.1.e). When reacting α-halogen amides with inorganic iso(thio)cyanates (highlighted, *Fig. 4f*), N-1 unsubstituted hydantoins are generated (chapter I.1.f).

Synthetic Strategies and Building Blocks in Hydantoin Formation

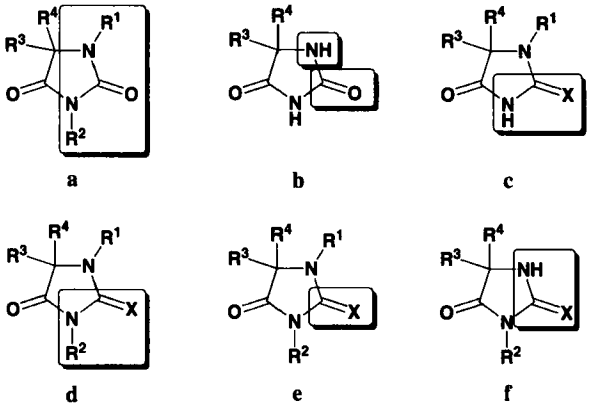
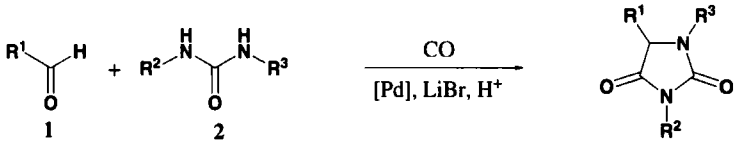


Fig. 4

a) From Carbonyl Compounds and Ureas

i) From Monocarbonyl Compounds or Carbon Dioxide and Ureas

A new one-pot synthesis for the preparation of hydantoins was developed by Beller *et al.*[42] Reacting different aldehydes with various ureas and carbon monoxide under palladium catalysis afforded mono-, di- and trisubstituted hydantoins **3** (*Scheme 1*). 1,3,5-Trisubstituted



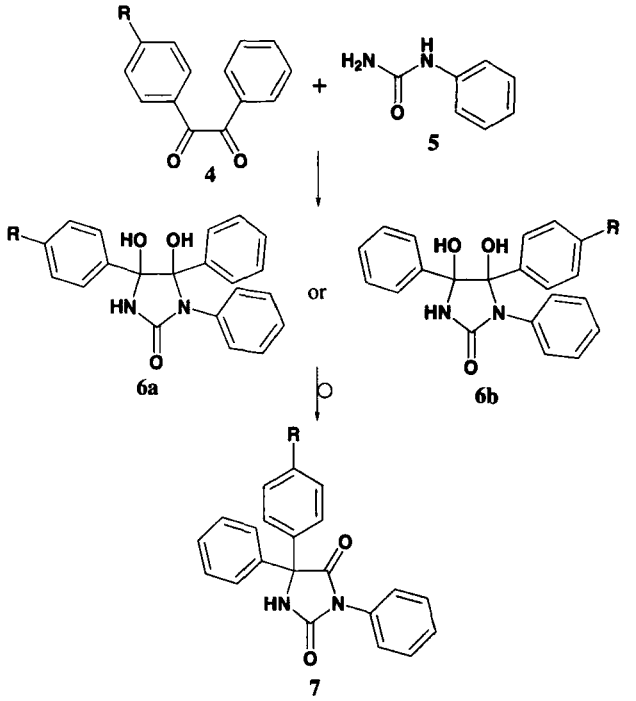
Scheme 1

hydantoins could be obtained from *N*-benzyl-*N,N'*-dimethylurea and *sec*-BuLi/TMEDA followed by CO_2 treatment.[43] Monosubstituted ureas also gave hydantoins when treated with α-keto hemithioacetals, the latter obtained from a Pummerer rearrangement of a β-ketosulfoxide.[44]

ii) From α-Dicarbonyl Compounds and Ureas

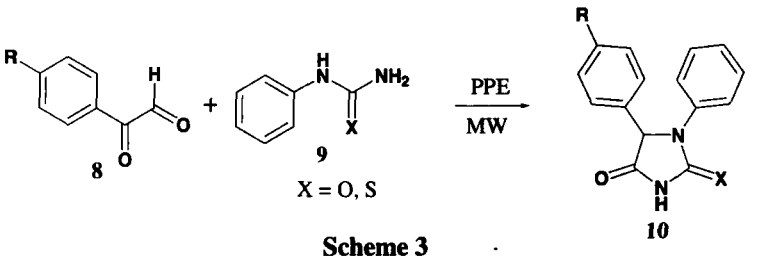
Even nearly hundred years after its introduction, the Biltz synthesis is still of value for the preparation of hydantoins (*Scheme 2*), and the mechanism of this rearrangement has been recently investigated by mass and NMR spectroscopy with ^{13}C labelled benzil derivatives.[45] Recently new technologies, such as microwave-assisted synthesis, have been applied to this common synthetic pathway in order to improve yield and reaction time. Phenytoin and phenytoin

derivatives were synthesized by irradiating an alkaline mixture of (thio)ureas and benzils in DMSO with 750 W microwave pulses.[46]



Scheme 2

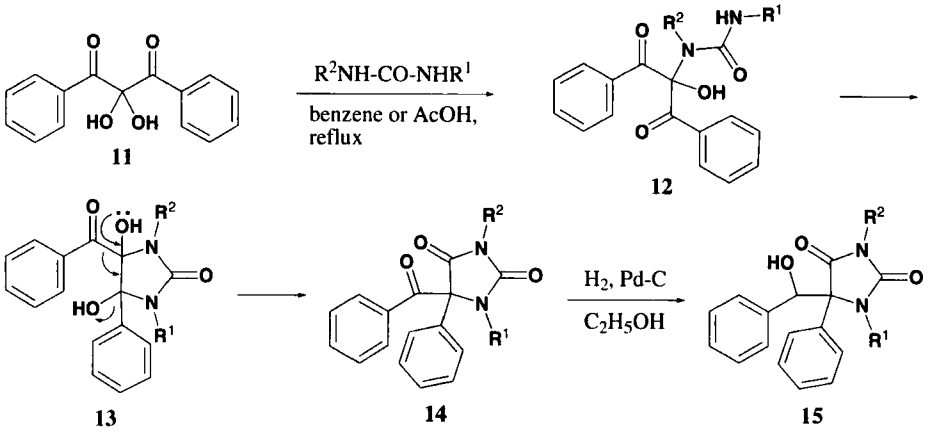
Paul and coworkers[47] accomplished a solvent-free microwave-assisted synthesis of disubstituted hydantoins and thiohydantoins **10** (*Scheme 3*). Thus, arylglyoxals **8** were reacted with phenylurea or phenylthiourea and polyphosphoric ester as reaction mediator. Moreover, the



Scheme 3

use of phenylglyoxal and adamantylurea gave 1-adamantyl-5-phenylhydantoin, which showed anticonvulsant activity.[2b] Reaction of pyruvaldehyde or phenylglyoxal with *N*-methyl-*N'*-substituted ureas afforded 3-substituted 1-methyl-5-methyl(phenyl)hydantoins.[48]

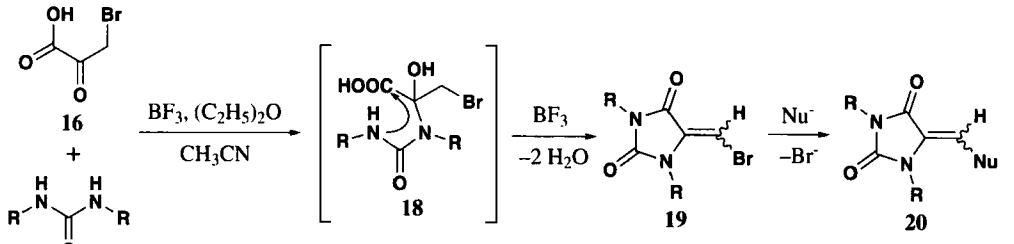
If diphenyltriketone hydrate **11** was subjected to such a pinacol-pinacolone-type rearrangement reaction with different ureas, 5-benzoyl-5-phenylhydantoins **14** were obtained (*Scheme 4*).[49] Interestingly, even C-5 unsaturated hydantoins could be prepared from α-dicarbonyl compounds and ureas though the pathway follows an addition-elimination mechanism.[50]



11 12 13 14 15

Scheme 4

As shown in *Scheme 5*, bromopyruvic acid **16** was condensed with ureas to give 5-(bromomethylene)hydantoins **19**, which were then reacted with nucleophiles to generate the desired hydantoins **20**.



16 + 17 18 19 20

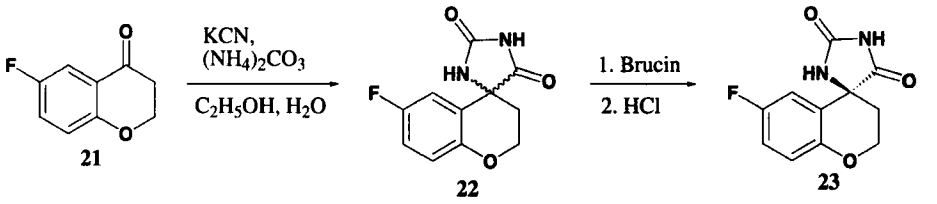
Scheme 5

In a one-pot synthesis 1,3-benzodioxole-5-thiol, glyoxylic acid, and urea were condensed to a 5-sulfanylhydantoin.[51] The use of solid acids was described to promote the direct synthesis of 5-(4-hydroxyphenyl)hydantoin from phenol, urea and glyoxylic acid.[52]

There are other reactions between α-dicarbonyl compounds and ureas building hydantoin derivatives which deviate from the mechanism of the Biltz synthesis. Ishii and coworkers illustrated the condensation of oxalyl chloride with monosubstituted ureas to form 2,4,5-trioxoimidazolidines, which represent substituted parabanic acids.[53] Ring opening of a carbamoylisatin derivative by urea gave the oxalylurea analogue, which could be cyclized in two different mechanisms: (i) first generating the quinazolin-2-one unit and followed by formation of the hydantoin ring under acidic conditions or (ii) first forming the hydantoin moiety and followed by generation of the quinazolin-2-one ring using primary amines.[54]

b) Methods Based on the Bucherer-Bergs Synthesis

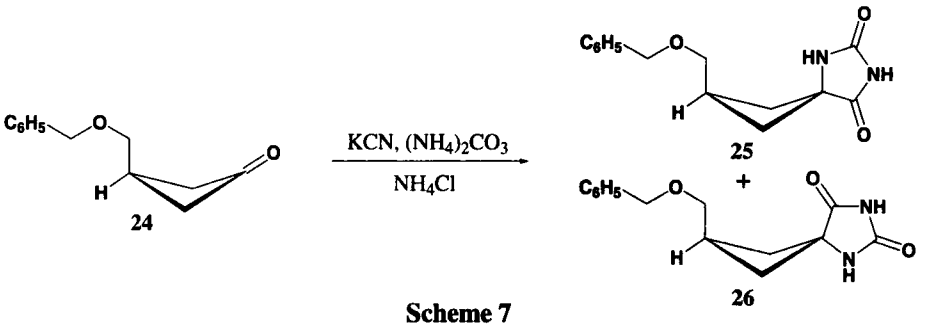
Because of the relative ease of execution, the Bucherer-Bergs synthesis is a practical and suitable route to provide hydantoins. It is remarkable how often this classical synthetic methodology is still employed nowadays to create hydantoins for a wide range of applications,[15b,55-58] including carbohydrate chemistry.[59] The synthesis embraces the reaction of carbonyl compounds with potassium cyanide and ammonium carbonate. These standard conditions remained unchanged during the last decades. Sarges *et al.* used this synthetic pathway starting from benzopyranone **21** to prepare the aldose reductase inhibitor sorbinil **23** (*Scheme 6*),[15a] and



21 22 23

Scheme 6

Martarello and coworkers generated PET ligands for tumor detection *via* hydantoins **25** and **26** (*Scheme 7*).[60]

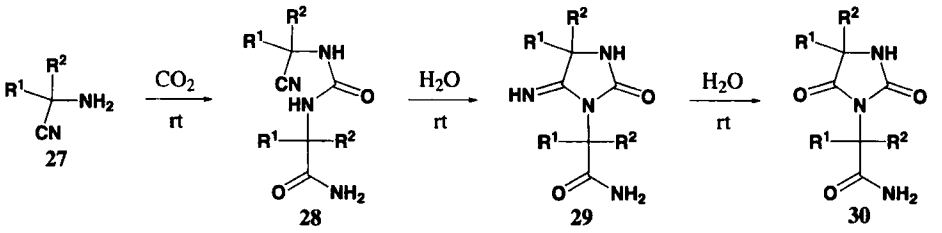


24 25 + 26

Scheme 7

Accordingly, 2,3-dihydro-1*H*-quinolin-4-ones have been transformed by Bucherer-Bergs method resulting in spirohydantoins, which act as ligands at somatostatin receptors.[61] The procedures described by Comber *et al.* disclosed a dithionation of the hydantoin scaffold as well as the introduction of two sulfide moieties into the side chains.[21a]

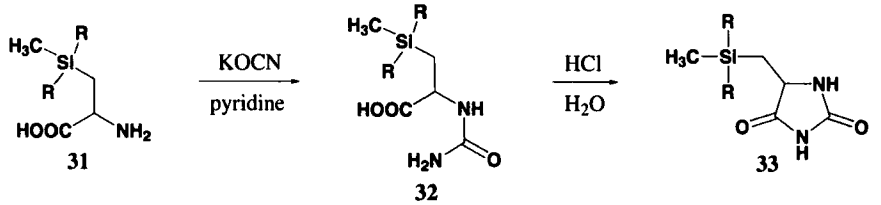
It was found that ultrasonication could accelerate hydantoin formation using the Bucherer-Bergs reaction.[62] Uhrich *et al.*[63] and O'Brien *et al.*[64] treated α-amino nitriles with carbon dioxide to give the disubstituted ureas **28** which underwent cyclization in water at room temperature followed by hydrolyzation of the imino compounds **29** to the corresponding hydantoins **30** (*Scheme 8*). However, α-amino nitriles **27** are generally accepted as intermediates in the Bucherer-Bergs synthesis which produces 1,3-unsubstituted hydantoins[1] instead of the products **30**.



Scheme 8

c) Methods Based on the Read Synthesis

A second long-known and frequently applied[13,18b,65] preparation of (thio)hydantoins is the Read synthesis. During their efforts to obtain silicon-containing hydantoins, Smith *et al.* treated silylated amino acids **31** with potassium cyanate in pyridine followed by acid cyclization (*Scheme 9*).[66] *N*-(*p*-Toluenesulfonyl)amino acids were cyclized with NH_4SCN to 1-(*p*-toluenesulfonyl)thiohydantoins.[67]

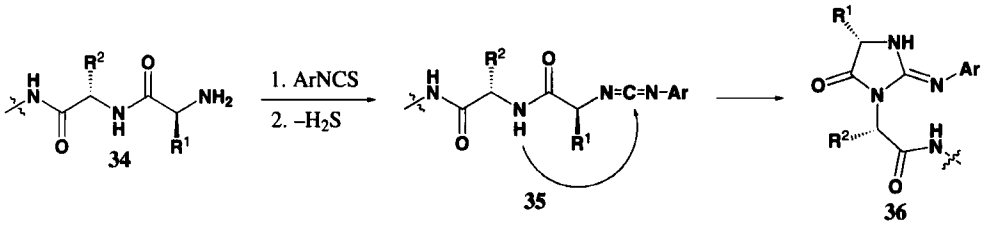


Scheme 9

Similar approaches have been reported by Anteunis and coworkers, employing α-methyl phenylalanine in their investigations on enantiomeric pure and stable hydantoins for chiral amine synthesis. Other classical methods, such as Bucherer-Bergs synthesis or hydantoin synthesis from amino acids and urea were also discussed in this report.[68] Access to the 5-methylenehydantoin was achieved by conversion of cystine *via* a double Read synthesis and cleavage of the dimer under standard alkylation conditions.[69]

d) From Amino Acids or Esters and Isocyanates

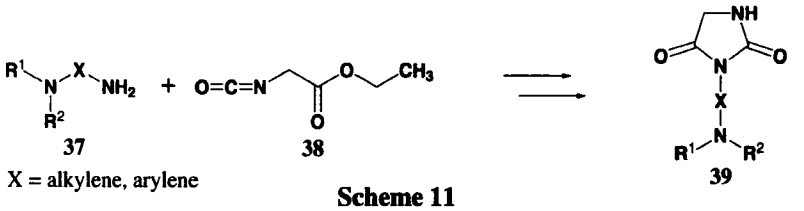
Hydantoins can be prepared by treatment of α-amino acids with aryl or alkyl isocyanates *via* the intermediate ureido acids. Esters or amides of α-amino acids and even peptides can also act as starting materials. The reaction of the terminal amino group with phenyl isothiocyanate represents the basis of the well-known Edman degradation for *N*-terminal sequence analysis of peptides. The Edman degradation was varied in a way that led to a heterocyclic modification of the *N*-terminus of a peptide.[70] Thus, the thiourea formed from the amino acid and the aryl isocyanate was subjected to a dehydrothiolation reaction, and subsequent trapping of the intermediate carbodiimide **35** by the adjacent amide nitrogen resulting in a small library of 2-iminohydantoins **36** (*Scheme 10*).



Scheme 10

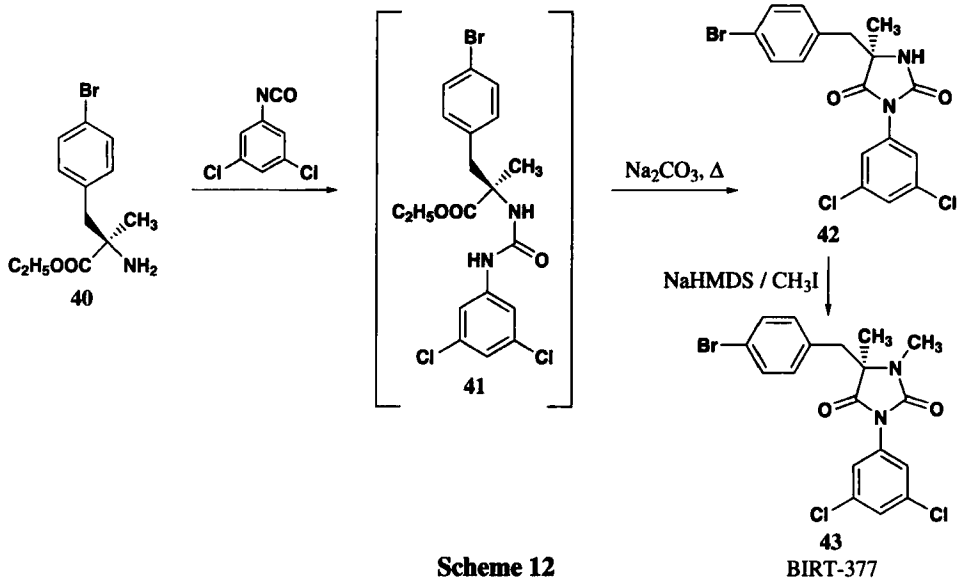
In contrast to the Edman method, Schlack and Kumpf developed a C-terminal stepwise peptide degradation. Treatment with ammonium thiocyanate and acetic anhydride leads to the formation of 1-peptidyl-2-thiohydantoins and the subsequent hydrolytic release of the thiohydantoin.[71]

Examples reported by Lopez and Trigo[1] only embraced acid-catalyzed cyclizations of the ureido compounds. This method was used in recent works[72] including those that generated (thio)ureas from (ethoxycarbonyl)methyl isocyanate **38** and primary amines such as mono- or dialkyldiamines **37** (*Scheme 11*).[73]



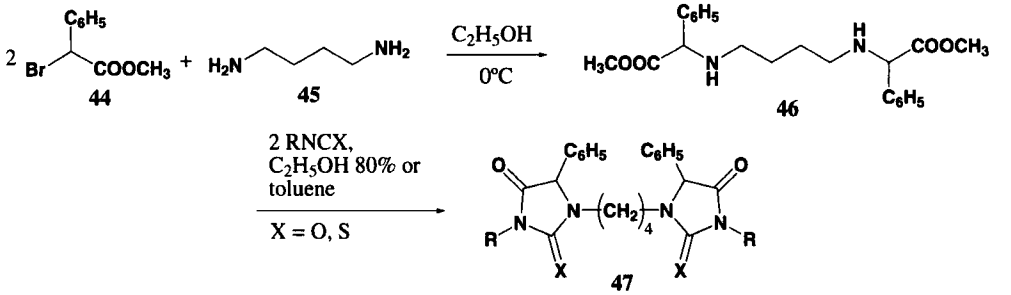
Scheme 11

On the other hand, there are some new examples for base-mediated cyclization.[2j,74-78] The synthesis of the LFA-1 antagonist BIRT-377 *via* the intermediate urea **41** is shown in *Scheme 12*.[10c]



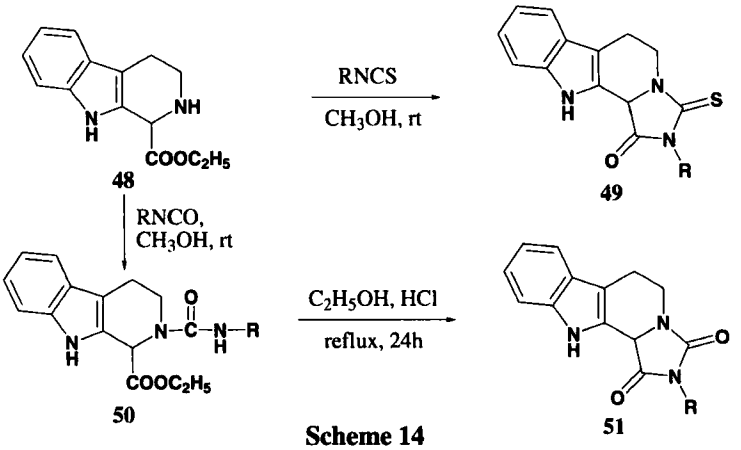
Scheme 12 BIRT-377

An intriguing solution-phase synthesis of a 600 member (thio)hydantoin library was reported by Sim and Ganesan. *N*-Alkylation of amino acid esters was accomplished by imine formation with aldehydes and reduction, followed by addition of iso(thio)cyanate together with triethylamine leading to trisubstituted products.[75] Similar approaches employing (ethoxycarbonyl)methyl isocyanate provided hydantoins with integrin GP IIb/IIIa antagonistic properties[4c,79] or aldose reductase inhibitors.[15f] A series of indolylmethyl hydantoins showing a good affinity on the NMDA glycine site were synthesized by cyclization with triethylamine.[80] The preparation of *bis*-hydantoins separated by two and four-carbon spacers (*Scheme 13*) was reported.[81]



Scheme 13

Moreover, the reaction of amino acid derivatives with isocyanates could be transferred to amino acids being part of different polycyclic ring systems[77] such as 1,2,7,7a-tetrahydro-1a*H*-cyclopropa[*b*]quinoline-1a-carboxylic acid,[82] tetrahydroisoquinoline-3-carboxylic acid,[76] 2-azabicyclo[2.2.1]hept-5-ene-3-carboxylic acid[83] or tetrahydro-β-carboline-1-carboxylic acid (*Scheme 14*)[84] and -3-carboxylic acid, the latter prepared from tryptophan esters and aldehydes

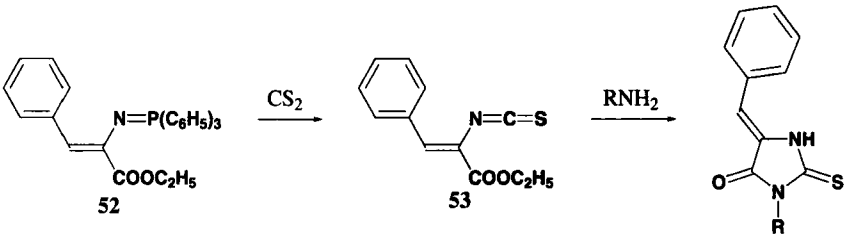


Scheme 14

via a modified Pictet-Spengler reaction.[14,85] A hydantoin C-nucleoside was prepared by a route involving the reaction of phenyl isocyanate with a tricyclic lactam ester serving as a ribose precursor.[86]

Exploration of synthetic strategies to form spirohydantoins provided the implementation of microwaves[77] and cycloaddition reactions.[87] Isocyanates can be generated *in situ* from *N*-aryltrichloroacetamides in a strongly alkaline medium and react with amino acids or their esters to give ureido derivatives or directly the corresponding hydantoins.[88]

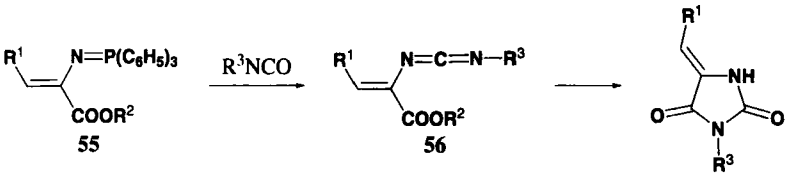
If the easily accessible vinyliminophosphorane **52** (*Scheme 15*) is treated with carbon disulfide followed by reacting the resulting vinyl isothiocyanate **53** with primary amines, 5-benzylidene-2-thioxo-imidazolidinones **54** were obtained.[89]



52 53 54

Scheme 15

Shiozaki reported syntheses of hydantocidin. One included the transformation of isothiocyanates to hydantoins *via* thiohydantoin intermediates. Another pathway embraced an aza-Wittig reaction to a carbodiimide, which was transformed to urea derivatives. Cyclization with an adjacent ester group and deprotection of the monosaccharide moiety completed this route.[90] A similar approach demonstrated the aza-Wittig reaction of iminophosphoranes from dimethyl dehydroaspartate (**55**, R^1 = $COOCH_3$, R^2 = CH_3) with isocyanates (R^3 = C_2H_5, $CH_2CH_2CH_3$, C_6H_5) to give carbodiimides **56**, which were readily converted to hydantoins **57** (*Scheme 16*).[91] A



55 56 57

Scheme 16

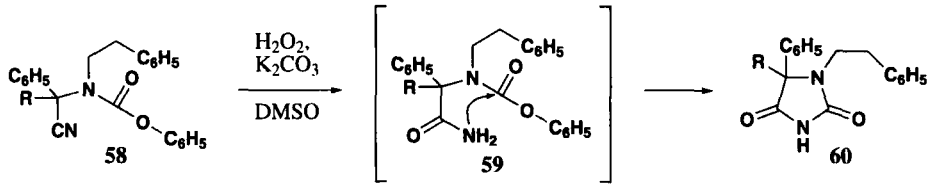
further example involved iminophosphoranes in the synthesis of azaaplysinopsins.[5e] Isocyanates (R^3 = C_2H_5, C_6H_5) were reacted with compounds **55** (R^1 = azaindolyl, R^2 = C_2H_5) in toluene to give carbodiimides which were cyclized to the corresponding hydantoins (*Scheme 16*). Different mechanisms for this reaction were postulated.

A series of (thio)hydantoins was prepared from α-azidocarboxylic esters by a method based on the Staudinger reaction.[92]

e) From Amino Acid Amides and Carbonic Acid Derivatives

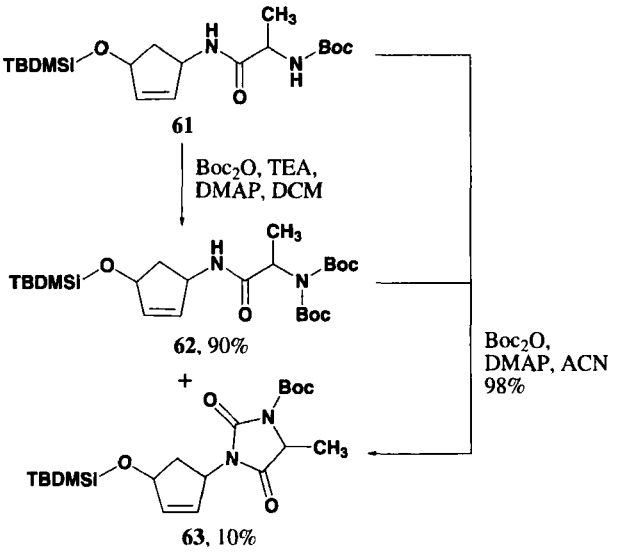
Amino acid amides open a further possibility to obtain hydantoins.[10d,70] Coupling Boc-protected amino acids to primary amines and subsequent deprotection afforded the desired amino acid amides, which could then be cyclized with carbonyldiimidazole (CDI).[21e,93] This cyclization strategy has often been used in solid-phase synthesis (see I.2.b).

Amidines[94] and amino acid amides[95] were treated with 4-nitrophenyl chloroformate to introduce a C=O unit. In the latter case, the formation of intermediate isocyanates was postulated for the subsequent hydantoin cyclo-condensation. A similar hydantoin forming cyclization of an α-cyano amide **58** with excess of basic hydrogen peroxide *via* a carbamate intermediate was shown in a study on the reactivity of open-chain Reissert compounds (α-acylaminonitriles **58**, *Scheme 17*).[96]



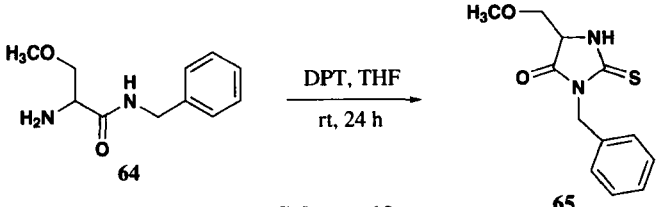
Scheme 17

An attempted protection of amino acid amide **61** with Boc_2O promoted hydantoin formation with the incorporation of one Boc-carbonyl into the ring (*Scheme 18*).[97]



Scheme 18

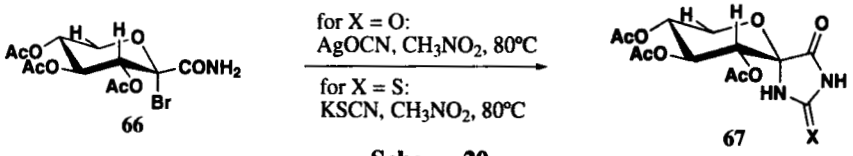
Thiohydantoins were available from amino acid amides and carbon disulfide.[93] LeTiran and coworkers prepared thiohydantoins by the treatment of **64** with di-2-pyridylthiocarbonate (*Scheme 19*).[2j]



Scheme 19

f) Miscellaneous Conversions of Carboxamides

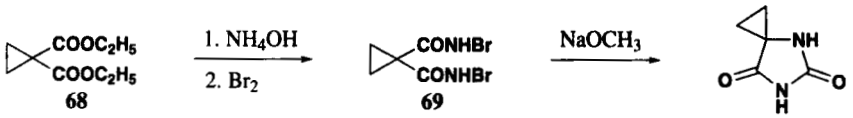
As in the Read synthesis, inorganic (thio)cyanates could be applied in a hydantoin preparation shown in *Scheme 20*. Instead of amino acids, bromo amide **66** was thereby transformed to glycopyranosylidene-spiro-(thio)hydantoins **67**.[15h]



66 67

Scheme 20

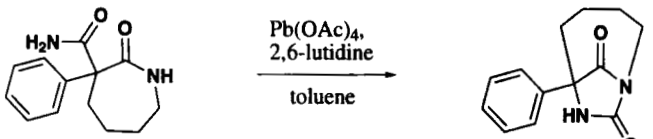
Cyclopropane dicarboxylic acid derivatives **68** underwent a Hofmann rearrangement to form 1,3-unsubstituted hydantoins (*Scheme 21*).[98]



68 69 70

Scheme 21

The synthesis of a bicyclic hydantoin containing an imide bridgehead nitrogen was accomplished with 3-(aminocarbonyl)-3-phenylhexahydro-2*H*-azepin-2-one **71** (*Scheme 22*) as



71 72

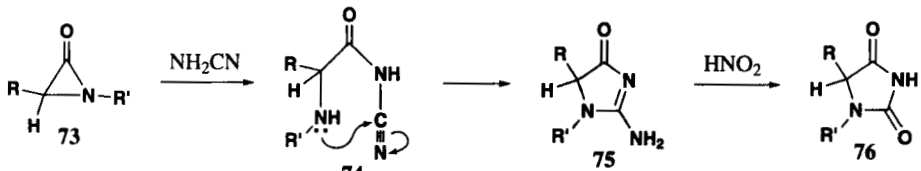
Scheme 22

starting compound.[108] After formation of an isocyanate by a Hofmann rearrangement, an intramolecular attack of the lactam nitrogen gave 1,7-diaza-8,9-dioxo-6-phenyl-bicyclo[4.2.1]nonane **72**.

g) Conversions of Other Heterocyclic Compounds to Hydantoins

i) Conversion Reactions from Three-Membered Rings

1,5-Disubstituted hydantoins **76** could be prepared from reacting aziridinones **73** with cyanamide and treatment of the formed iminohydantoins **75** by HNO_2 (*Scheme 23*).[99]

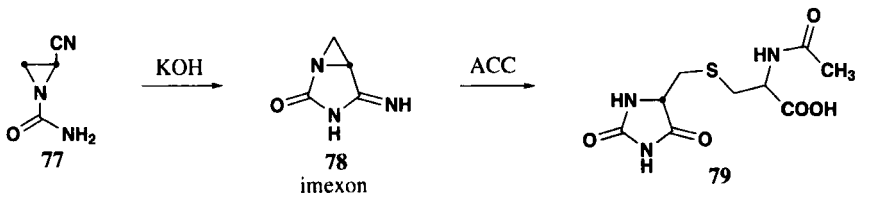


73 74 75 76

Scheme 23

Cyanoaziridine **77** was subjected to basic conditions to give the bicyclic imexon, containing an iminohydantoin moiety (*Scheme 24*).[100] Efforts have been focused on reaction of

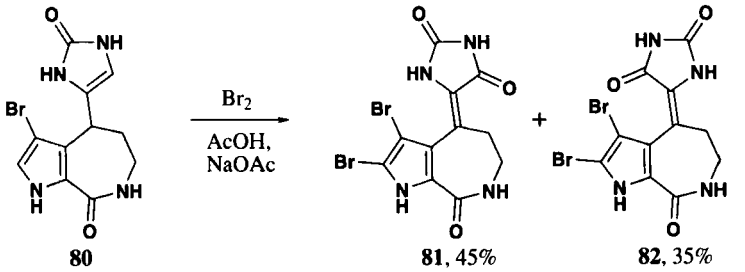
the antitumor agent imexon with cysteine and *N*-acetylcysteine. Depending on the reaction conditions, thiazolines or (imino)hydantoins were generated.



Scheme 24

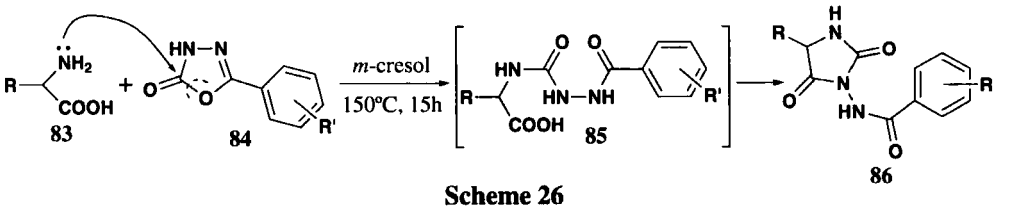
ii) Conversion Reactions from Other Five-Membered Rings

Of interest with respect to the transformation of other five-membered rings to hydantoins are investigations on the synthesis of naturally occurring compounds with a hydantoin moiety. Sosa and coworkers[28] prepared pyrroloazepinones containing a 2-imidazolone substituent that were then oxidized by three equivalents of bromine to afford the axinohydantoin derivatives **81** and **82** (*Scheme 25*).



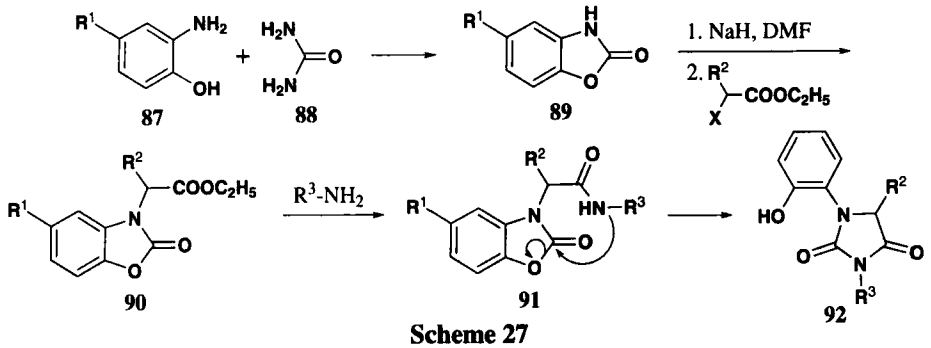
Scheme 25

2-Aminooxazoles also can rearrange to hydantoins in the presence of bromine.[101] 1,3,4-Oxadiazolinones **84** were the starting materials in a one step reaction with free α-amino acids leading to disubstituted hydantoins **86** (*Scheme 26*).[102]



Scheme 26

A practical route to 1-(2-hydroxyphenyl)-2,4-imidazolidinediones **92** has been demonstrated through cyclic transformations of ethyl 2-oxo-3*H*-2-benzoxazoloneacetate **90** by reaction with ammonia, primary amines (*Scheme 27*) or hydrazines. A subsequent intramolecular nucleophilic attack of the amido nitrogen at the benzoxazolone carbonyl group with a concomitant ring opening gave the hydantoins.[103]

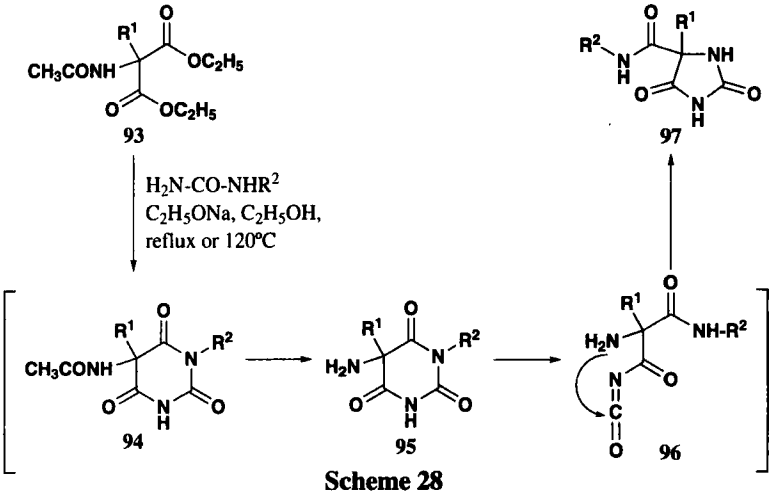


Scheme 27

iii) Ring Contraction Reactions from Six-Membered Rings

Many ring contraction reactions from six-membered rings to hydantoins started from pyrimidine derivatives, such as barbiturates or orotates. A photochemical conversion of 5-allyl(ethyl)-1-methyl-5-phenylbarbituric acid to 5-allyl(ethyl)-3-methyl-5-phenylhydantoin was described, the reactions involved the loss of carbon monoxide.[104] Methyl dihydroorotate underwent a methoxide-catalyzed transformation to methyl hydantoin-5-acetate. Dimethyl 2-ureidosuccinate was proposed as a ring-opened intermediate, thus the exocyclic ester moiety served as an electrophile for the recyclization.[105]

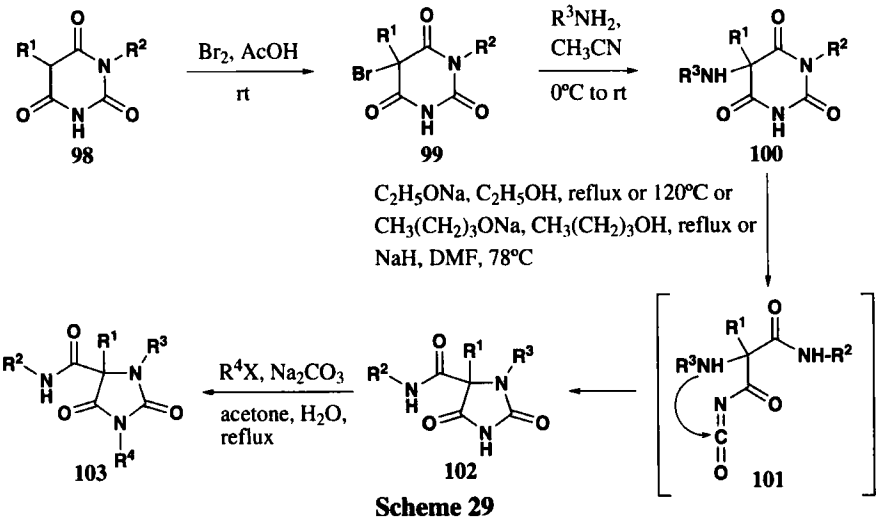
Another approach is based on the new aminobarbituric acid-hydantoin rearrangement.[106,107] First, diethyl acetamidomalonates were treated with ureas and formed the intermediate 5-acetaminobarbituric acids **94**, which underwent the rearrangement to yield 5,5-disubstituted hydantoins **97** in a one-pot synthesis (*Scheme 28*).[106]



Scheme 28

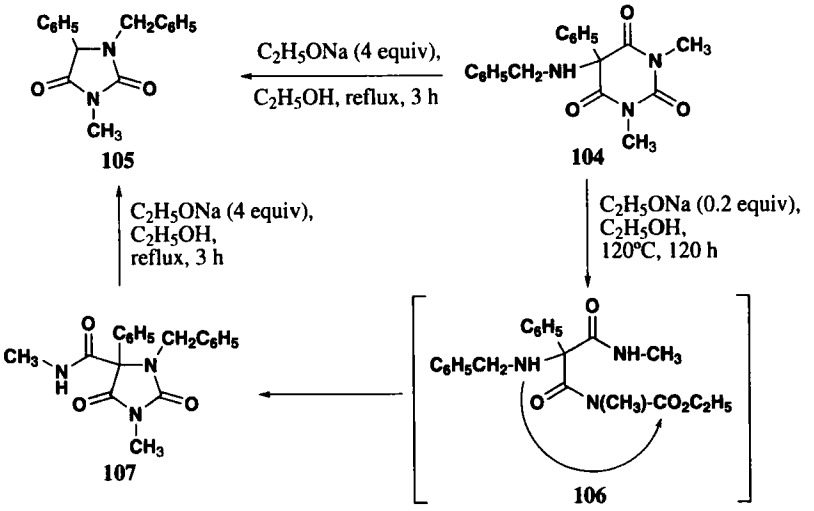
Further study of this rearrangement provided evidence that the rearrangement could also be performed starting from 5-aminobarbituric acids (*Scheme 29*). If 1,5,5-trisubstituted aminobarbituric acids **100** were used, the alkaline medium led to a deprotonation in position N-3

followed by elimination of an isocyanate **101**, which was subsequently trapped by a nucleophilic attack of the amino group.[106,107]



Scheme 29

In the case of 1,3,5,5-tetrasubstituted aminobarbituric acids, deprotonation is not possible and therefore the hydantoins could only be formed *via* a carbamate intermediate in an ANRORC-type reaction (*Scheme 30*). Treatment of aminobarbituric acid **104** with four equivalents of sodium ethoxide gave the trisubstituted hydantoin **105**. This could be explained by an

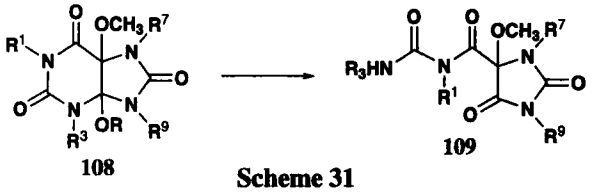


Scheme 30

easy decarbamoylation associated with additional N-3 substitution of the intermediate **107**. Therefore catalytic amounts of ethoxide had to be applied for the isolation of the 5-carbamoylhydantoin **107**.[107]

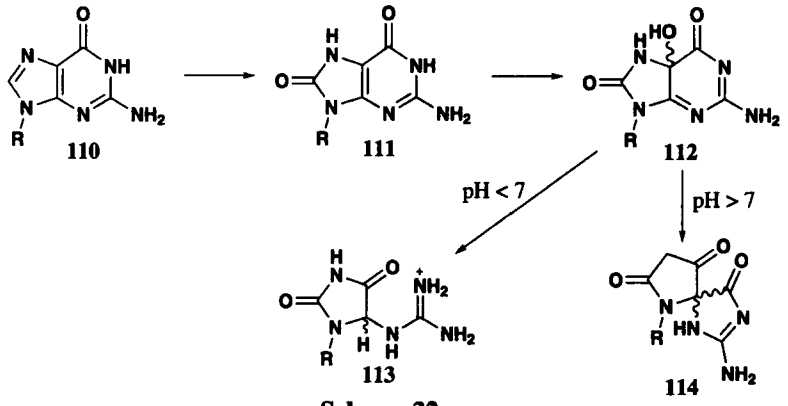
iv) Conversion Reactions from Purines

In connection with metabolic transformation reactions of purine such as uric acid derivatives or guanosine, hydantoin products have been found and characterized. Depending on conformational effects associated with the *N*-substitution of the uric acid derivatives **108** (R = CH_3, *Scheme 31*), hydantoins **109** could be obtained from acid-catalyzed reactions.[109] Ring opening was assumed to occur *via* acid-aminal type intermediates **108** (R = H).



Scheme 31

Oxidation of guanosine by singlet oxygen plays an important role *e.g.* in cancer etiology. Investigations of this process led to the recognition of guanidinohydantoins **113** and spiroiminodihydantoins **114**[110] as potential products of double stranded DNA and nucleosides, respectively (*Scheme 32*).[111]



Scheme 32

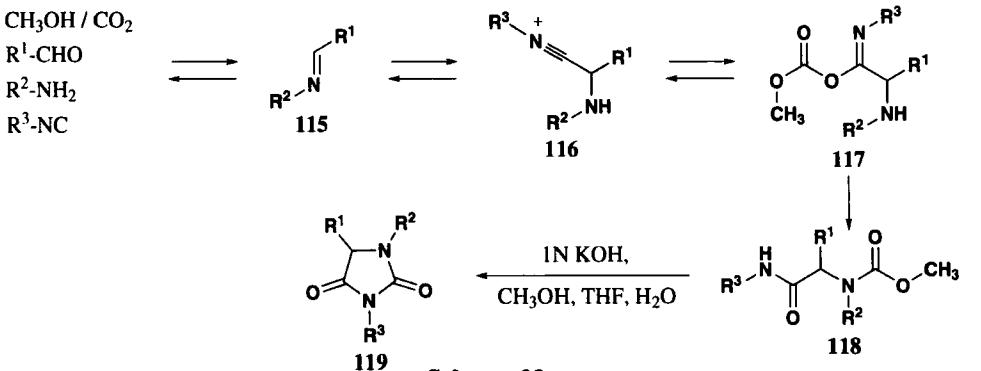
h) Cycloaddition Reactions

Although several publications described cycloadditions to generate hydantoin containing compounds[112-115] (see I.1.d and I.2.a), such reactions have been used only sparecely to construct the hydantoin core itself. This subject was explored by Lee *et al.*[116] who treated benzaldehyde 1-ureidoethylidene hydrazones with dimethyl acetylene dicarboxylate (DMAD) in dichloromethane (DCM) in the presence of triphenylphosphine, carbon tetrachloride and triethylamine. Two carbons of DMAD were incorporated in the hydantoin scaffold to form the CO-C5-unit.

i) Multi-component Reactions

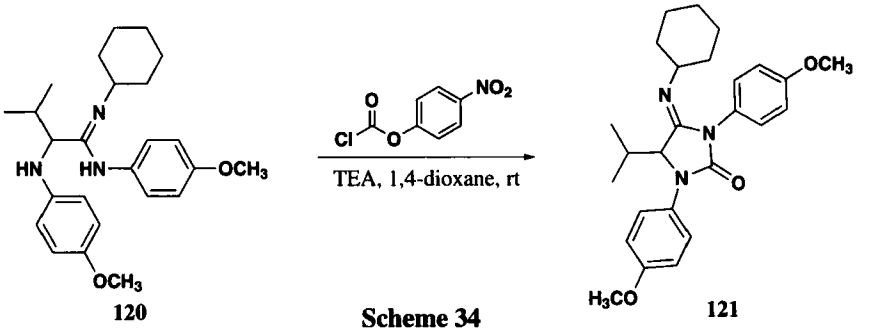
Utilizing the Ugi/De-Boc/Cyclization methodology, a facile synthesis of trisubstituted hydantoins was reported.[117] Aldehydes (or ketones), amines, isonitriles, methanol and carbon

dioxide acted as starting materials. The mechanism of this five-component reaction is shown in *Scheme 33*. The intermediate nitrilium ions **116** underwent an addition of methyl carbonic acid, generated from CO_2 and methanol. The following irreversible acyl transfer gave the carbamate compounds **118**. These carbamates were cyclized under alkaline conditions.



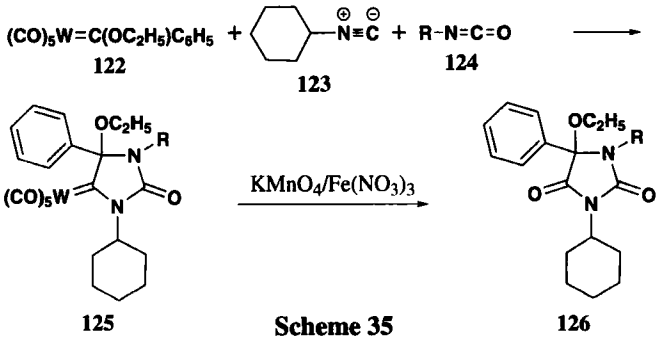
Scheme 33

N,N'-bis-(4-Methoxyphenyl)ethylenediamine, isobutyraldehyde and cyclohexyl isonitrile were reacted in the presence of scandium(III) triflate as catalyst to give the corresponding amidine **120** (*Scheme 34*), followed by iminohydantoin formation with *p*-nitrochloroformate.[94]



Scheme 34

Hydantoin complexes **125** were obtained by three-component condensation of cyclohexyl isonitrile **123** with phenylethoxycarbene-tungsten-pentacarbonyl **122** and isocyanates. Upon oxidative decomposition, such complexes gave 5-alkoxyhydantoins **126** (*Scheme 35*).[118]

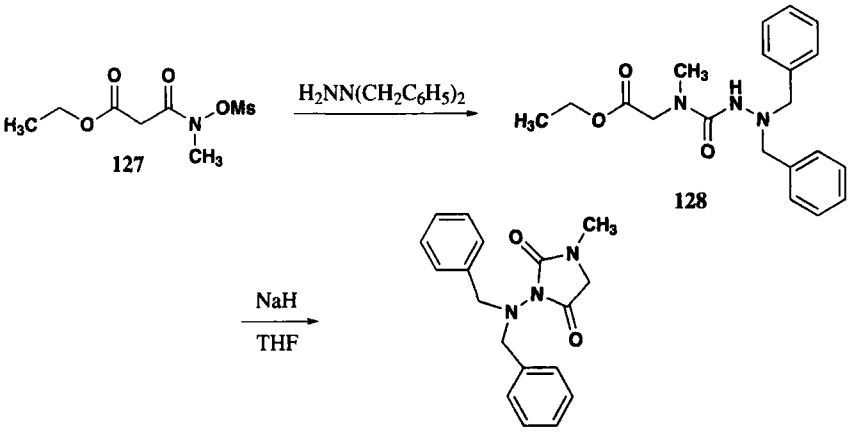


Scheme 35

k) Other Methods For the Synthesis of Hydantoins

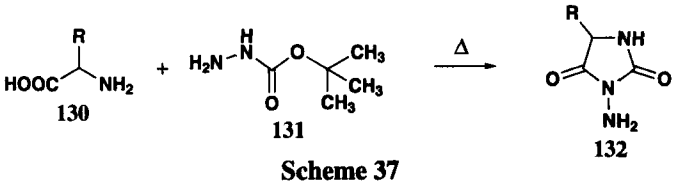
i) Syntheses of Aminohydantoins

A few synthetic strategies apply hydrazines to form 1- or 3-aminohydantoins.[16] Bélai treated *N*-acyl-*N'*-(1-cyanoalkyl)hydrazines with different isocyanates to afford substituted semicarbazides, which underwent a base-catalyzed intramolecular cyclization. Hydrolysis of the resulting imino compounds gave 1-aminohydantoins.[23] When *N*-mesyloxy-*N*-methyl-malonamic acid ethyl ester **127** was treated with *N,N*-dibenzylhydrazine (*Scheme 36*) or *N-tert*-butylhydrazine, respectively, 3-aminohydantoins were generated. The reaction involved the initial base-catalyzed formation of α-lactams, the attack of the hydrazines and subsequent ring closure.[120]



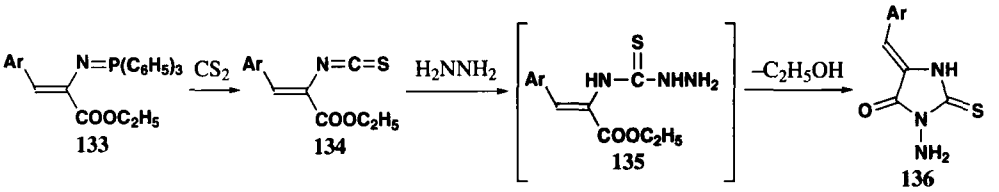
Scheme 36

Starting from amino acid derivatives, 3-aminohydantoins were synthesized in one-pot syntheses, using either 1,3,4-oxadiazolones[102] or *tert*-butyl carbazate **131** (*Scheme 37*).[121]



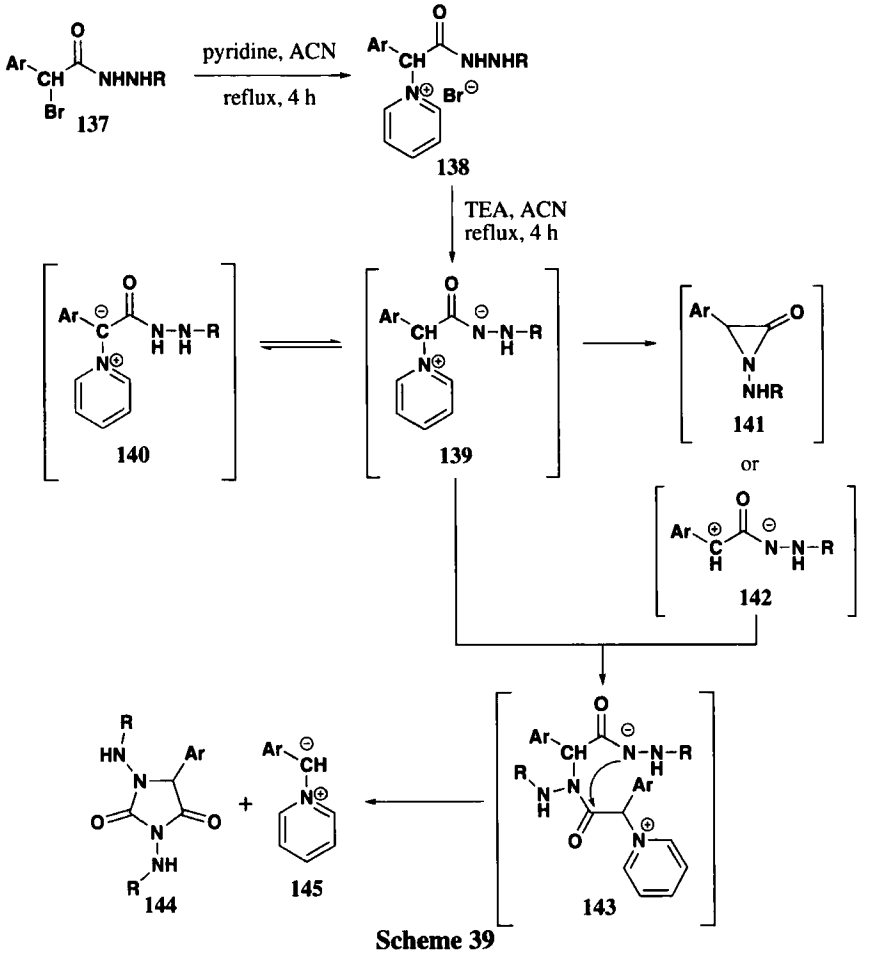
Scheme 37

Treatment of iminophosphoranes **133** with CS_2 and reacting the formed isothiocyanates **134** with hydrazine afforded 3-aminothiohydantoins **136** (*Scheme 38*).[192]



Scheme 38

The synthesis of 1,3-diaminohydantoins **144** was achieved by Florac *et al.* as shown in *Scheme 39*. α-Bromoarylacetohydrazides **137** were converted into the corresponding hydrazidopyridinium salts **138**. Upon treatment with triethylamine, the pyridinium salts underwent a Favorskii rearrangement to *N*-aminoaziridinones which were nucleophilically attacked by the pyridinium salts, followed by cyclization of the adduct.[122]

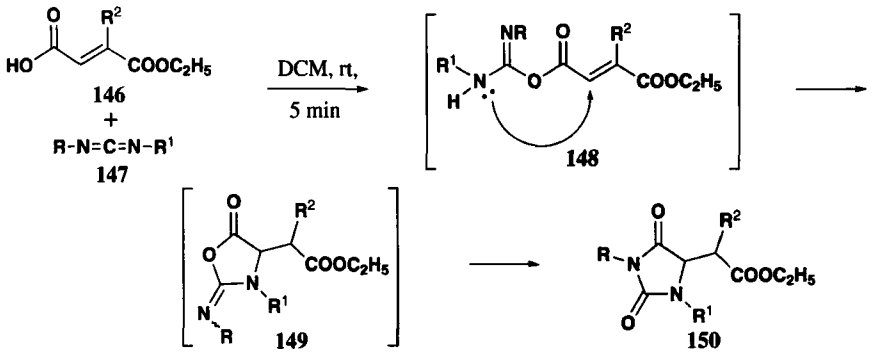


Scheme 39

5-Aminohydantoins were prepared by a route including reduction of parabanic acid, transformation of the resulting 5-hydroxyhydantoin to the chloro derivative, nucleophilic substitution with benzyl carbamate, alkylation and subsequent deprotection.[18a]

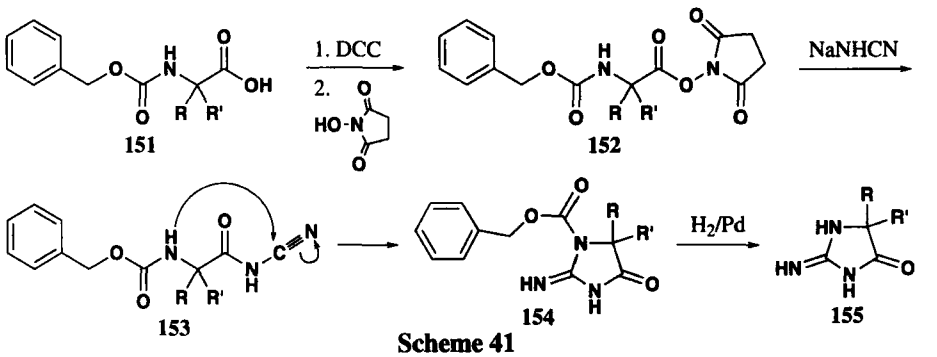
ii) Miscellaneous Syntheses of Hydantoins

Volonterio and Zanda reported a surprising hydantoin formation when α,β-unsaturated carboxylic acids were activated with carbodiimides *(Scheme 40)*.[123] Instead of the expected coupling products, iminooxazolidinones **149** were generated by an intramolecular aza-Michael addition of the unsaturated *O*-acylisoureas **148** and rearrangement to hydantoins **150**.



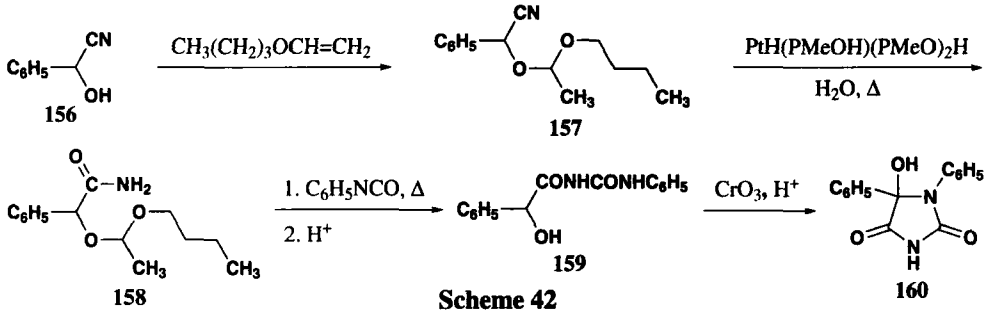
Scheme 40

Treatment of *N*-hydroxysuccinimide esters of carbobenzoxy amino acids **152** with excess sodium cyanamide gave *N*-protected aminoacylcyanamides **153**, which spontaneously cyclized to 2-iminohydantoins **154**. The protecting group was then removed by hydrogenation (*Scheme 41*).[119]



Scheme 41

Papakyprianou and coworkers provided an entry to 5-hydroxy-1,5-diphenylhydantoin by converting mandelonitrile **156** to *N*-mandelyl-*N'*-phenylurea **159** under protection of the hydroxy group by a mixed acetal (*Scheme 42*). After deprotection, **159** was cyclized to the aforementioned hydantoin by oxidation using chromium oxide in sulfuric acid.[124]



Scheme 42

Parabanic acid could be converted to 5,5-diarylhydantoins by triflic acid activated condensation with arenes.[125]

2. Solid-phase Organic Syntheses

Solid-phase synthesis of structurally diverse, non-peptidic heterocycles bearing one or more nitrogen atoms has recently attracted much attention. In particular, the synthesis of small organic molecules which have improved pharmacological properties over peptides has become a major focal point in search of leads utilizing automated high-throughput screening (HTS). The hydantoin scaffold is therefore quiet often selected as it provides a chemically tractable molecular framework. It allows a definite display of key functionalities and pharmacophores attached to the relatively rigid hydantoin core unit.

There are already some summaries on the field of solid-phase organic synthesis (SPOS) of hydantoins.[126] Herein we deemed it of interest to report the most recent efforts for preparing hydantoins by SPOS. The majority of these reactions started from dipeptides as acyclic precursors because of the considerable expertise that has been attained in solid-phase peptide synthesis (SPPS) since Merrifield's approaches in 1963.

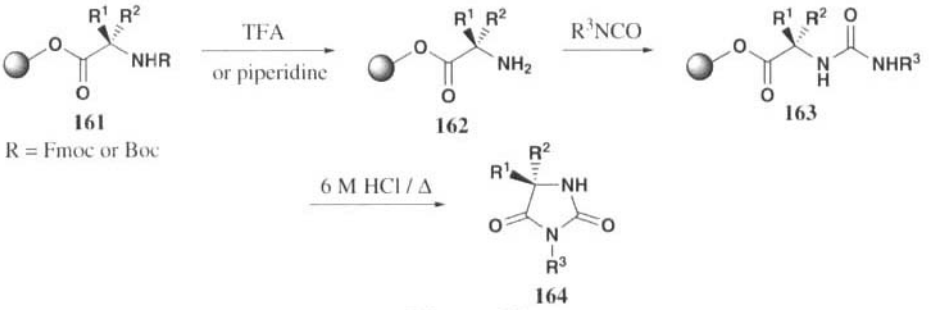
Cyclization and cleavage from the resin typically occurred in two ways: (i) by cycloelimination, that means cyclization of the acyclic resin-bound compound and spontaneous autocleavage and (ii) by performing cyclization and cleavage in separate steps. We therefore classified the reactions into these two main groups.

a) Cycloelimination Release Strategies

It should be pointed out that there is a review on the field of cycloelimination release strategies that also summarizes such cleavages in hydantoin formation.[127] Further reviews concerning solid-phase synthesis addressed the cyclative cleavage of heterocycles as well.[128]

i) Acid-catalyzed Cyclizations

DeWitt and coworkers were the first to report a synthesis of hydantoins on a solid support in 1993 using both a combinatorial and automated approach.[129] They prepared a library of 40 different hydantoins in a three step pathway outlined in *Scheme 43*. This strategy, starting



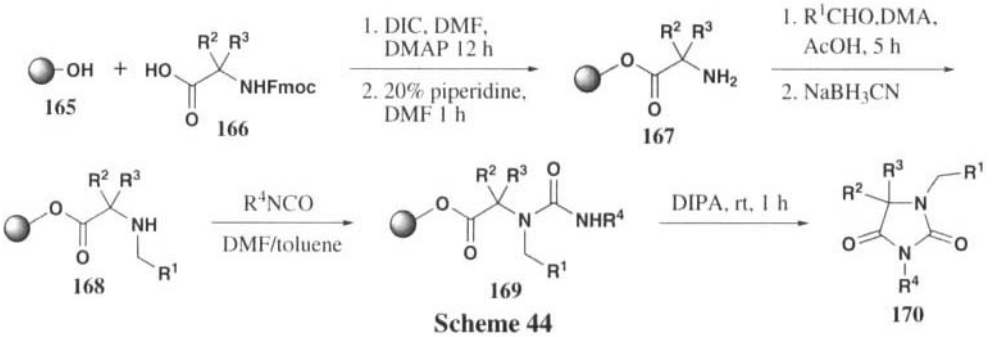
Scheme 43

from resin-bound amino acids **162**, followed by reaction with isocyanates, formation of the corresponding ureas **163**, cyclization to hydantoins **164** and cleavage, has become very common in solid-phase synthesis of hydantoins and thiohydantoins, respectively.

While DeWitt *et al.* used a polystyrene Wang resin, there are also reports employing other polymers. For example, acid-catalyzed cyclo-elimination release of hydantoins was performed on a 2-polystyrylsulfonyl ethanol support[130] or on high-loading radiation grafted polymers.[131] Differences between the reactivity of Wang *versus* Merrifield resins gave different results in the final cyclization step, especially when cleaved under basic conditions.[132]

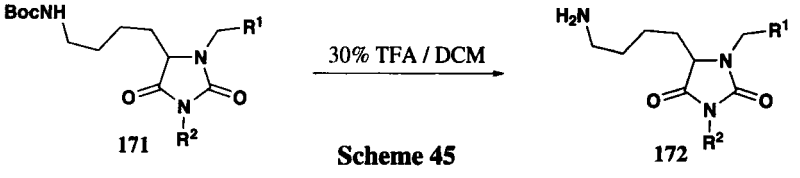
ii) Base-catalyzed Cyclizations

Analogous to the synthetic route employed by DeWitt *et al.* for the acidic cyclo-elimination[129], Kim *et al.* applied milder, basic cleavage conditions using neat diisopropylamine at room temperature (*Scheme 44*).[133] A reductive alkylation step was introduced *prior* to the reaction of the so prepared *N*-substituted resin-bound amino acids **168** with the isocyanates.



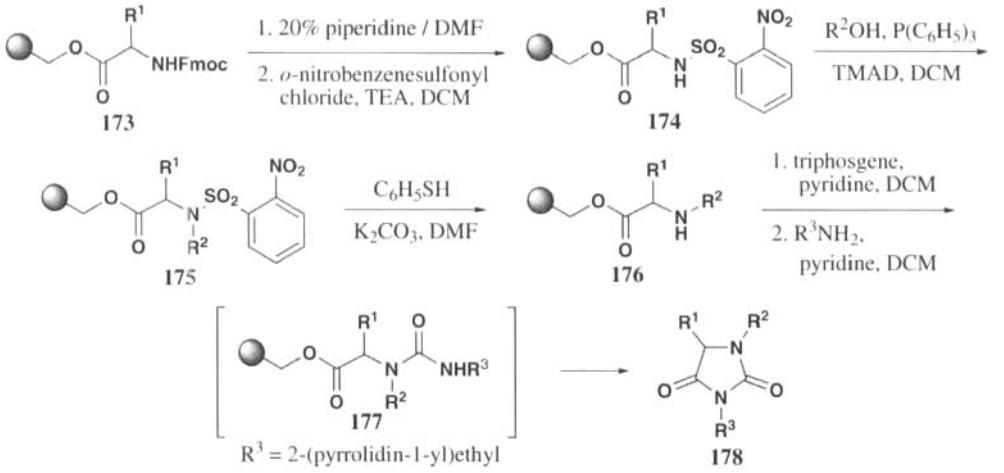
Scheme 44

Simultaneously, a similar procedure utilizing triethylamine for base-promoted cyclization was described by Matthews and Rivero.[134] Boeijen *et al.* have described this pathway on the more polar Tentagel®S-OH resin thereby performing the alkylation *via* a Mitsunobu reaction.[135] The procedures noted above included traceless cleavages, *i.e.* no residue of the linker was left on the released compound. Benzamidine and butylamine-based hydantoins have been prepared using neat diisopropylamine for delivering the product from the resin. The Boc protecting group was removed in a last step to produce **172** (*Scheme 45*).[136]



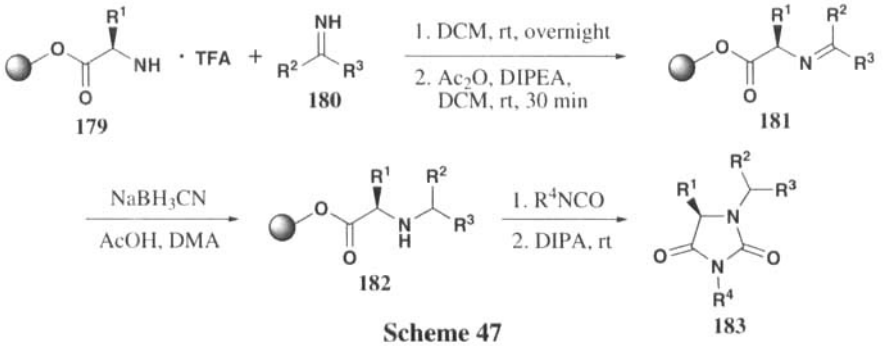
Scheme 45

A library of trisubstituted hydantoins was designed by a solid phase route employing amino acids, primary alcohols and amines as building blocks (*Scheme 46*).[137] With *N*-(2-aminoethyl)pyrrolidine as primary amine the basicity of the side chain led to cyclative autocleavage.



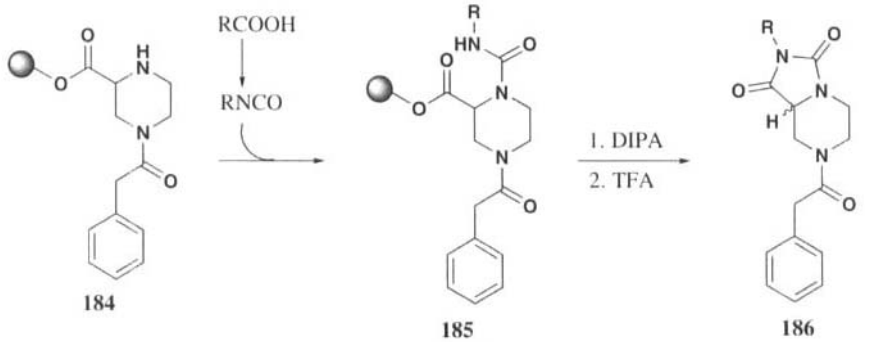
Scheme 46

A representative library of twenty hydantoins **183** was constructed from amino acids, N-H ketimines **180** and isocyanates (*Scheme 47*)[138] introducing additional diversity points by a step comparable to the reductive alkylation of *Scheme 44*.



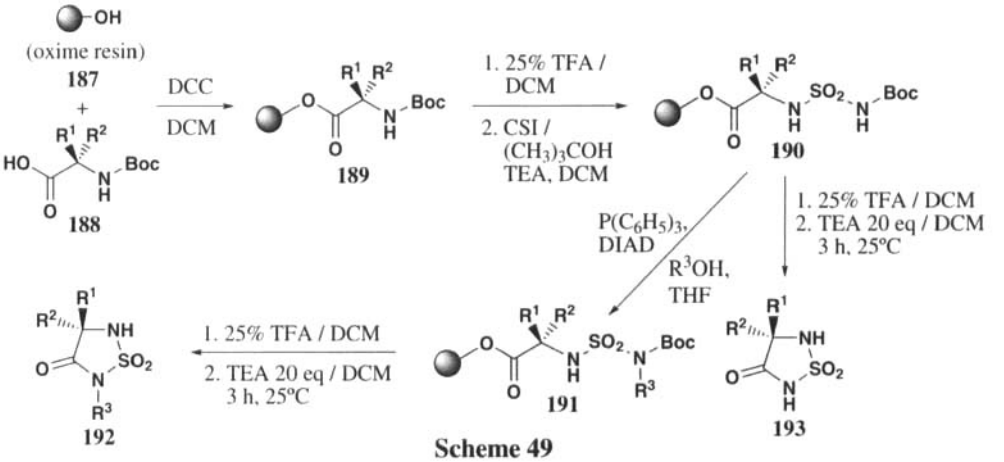
Scheme 47

Imidazo[1,5-*a*]pyrazines **186**, representing annelated hydantoin derivatives, have been synthesized employing the cyclocleavage reaction. The solid-phase synthesis of these heterocycles involved a solution-phase Curtius rearrangement of versatile carboxylic acids and the trapping of the formed isocyanates by the resin-bound amine **184** (*Scheme 48*).[139] Moreover, the



Scheme 48

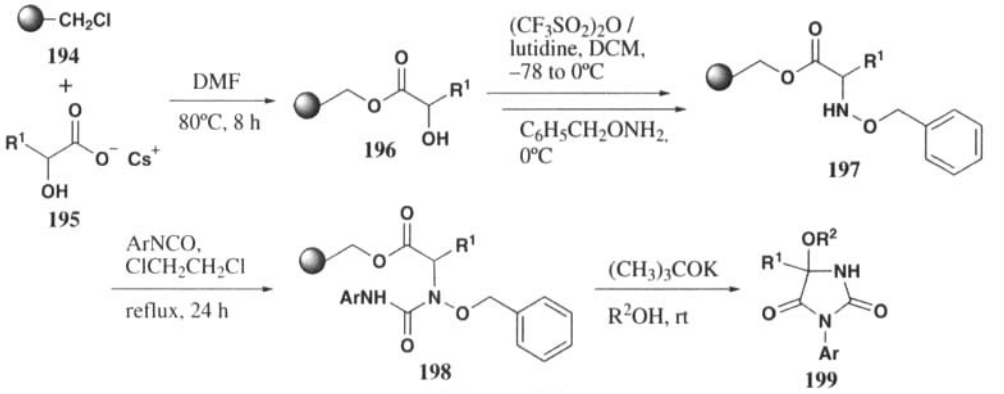
preparation of sulfahydantoins was accomplished on Wang resin[140] and on oxime resin[8b] using the bases DBU and triethylamine in the cleavage step, respectively. In the latter case, the sulfonyl group was introduced with chlorosulfonyl isocyanate (CSI), and optional alkylation to **191** was achieved *via* Mitsunobu reaction (*Scheme 49*).



Scheme 49

A structurally highly complex tricyclic triazacyclopenta[*c*]pentalene scaffold containing a hydantoin heterocycle was built up on a solid support in a 12-step reaction sequence including a [2+3] cycloaddition.[112] A solid-phase approach to hexahydro-1*H*-pyrrolo-[1,2-*c*]imidazole derivatives was accommodated from a developed solution-phase chemistry encompassing a tandem azomethine ylide cycloaddition.[141] Thus, the polycyclic hydantoins were formed from a benzylideneglycinate, which was bound to the resin *via* a spacer and underwent the cycloaddition. In both publications, base-promoted cyclization-autocleavage was described.

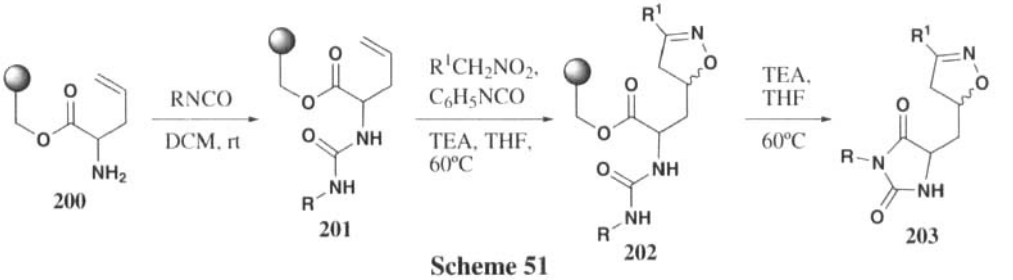
A general method producing 5-alkoxyhydantoins is shown in *Scheme 50*.[142] Treatment of polymer-bound ureas **198** with potassium *tert*-butoxide in different alcoholic solutions led to



Scheme 50

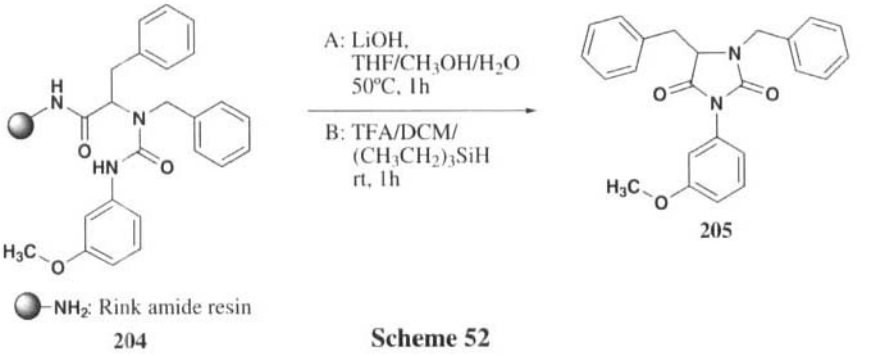
cyclization and detachment from the resin. The introduction of the alkoxy residue was proposed to result from an addition of the alcohol to an intermediate 3-arylimidazoline-2,4-dione.

Some interesting reports on the SPOS of molecules containing the hydantoin and an additional heterocycle, such as isoxazoline[113] (*Scheme 51*) or thiazole,[143] have been published. Aside from the cleavage strategy, the synthesis of the isoxazolylmethylimidazolidinediones **203** with a Mukaiyama-generated nitrile oxide is one more example for the application of a 1,3-dipolar cycloaddition on solid support.



Scheme 51

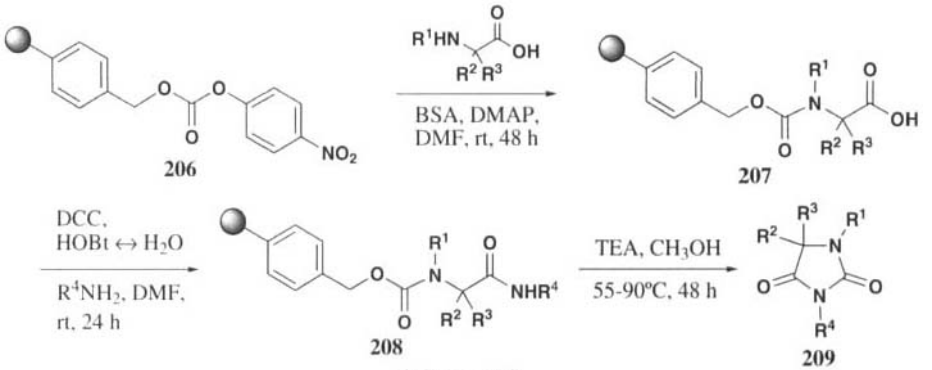
The described cyclization/cleavage strategies so far have always referred to a scission of an ester bond, however, it is also possible to release the hydantoin by cleaving an amide bond (*Scheme 52*).[17b] This could be successfully accomplished in basic or acidic medium. The starting



Scheme 52

amino acid was anchored to a Rink resin, and cyclative autocleavage could be performed under standard TFA conditions. Thereby, it was proposed, that not the NH-CH bond of the Rink linker was cleaved as usual, but the protonated amide NH caused a splitting of the NH-CO bond.

Further, amino acids have been attached to a solid support by a carbamate moiety.[144] Decisive for the function of the carbamate linker was the on-bead generation of an activated carbonate **206** *prior* to the coupling of the amino acid (*Scheme 53*). The carbamate nitrogen occupied the N-1 position in the formed hydantoin, and again cycloelimination cleavage worked under basic conditions.

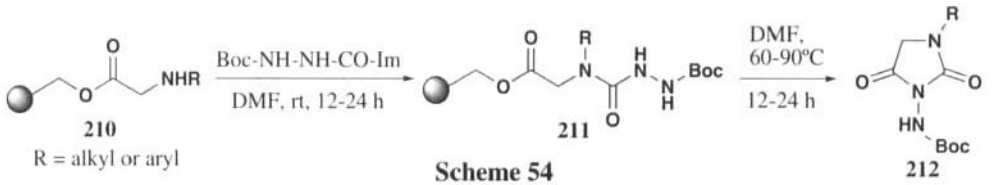


Scheme 53

iii) Thermal Cycloelimination Release Strategies

To simplify the introduction of pH-sensitive side chains to the hydantoin core and to prevent racemisation of chiral products in some cases, the cyclization of a polymer-bound (thio)urea and the following release of the (thio)hydantoin from the solid support could also be attained by gentle warming at 60 to 65°C.[114,115,145]

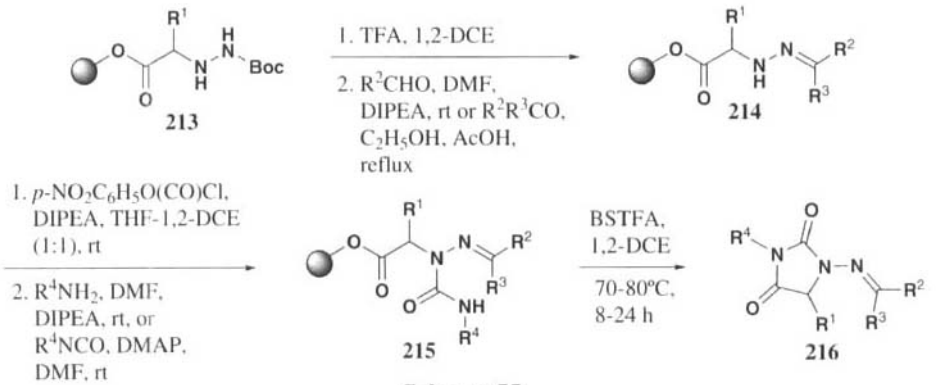
Boc-Hydrazine carbonylimidazole was applied in a SPOS of 3-aminohydantoins **212**, and the products were released by heating the resin-bound intermediates in DMF at 60 to 90°C (*Scheme 54*).[146]



Scheme 54

Hamuro and coworkers[147] attached amino acids to a Phoxime™ resin forming a carbamate linkage. Coupling of the terminal carboxyl group with mono- and disubstituted hydrazines and cyclo-elimination gave 3-aminohydantoins or triazinediones. Cleavage was carried out under basic conditions and mild heating.

Wilson *et al.* achieved the attachment of Boc-protected α-hydrazino acids to a hydroxymethyl polystyrene resin (*Scheme 55*).[148] The deprotected hydrazino-ester resins were converted into imines and then treated with *p*-nitrophenyl chloroformate and primary amines or isocyanates, respectively, to afford the corresponding ureas **215**. Cyclization to 1-aminohydantoin derivatives **216** occurred under mild neutral conditions using *bis*(trimethylsilyl)trifluoroacetamide (BSTFA) at 70 to 80°C.

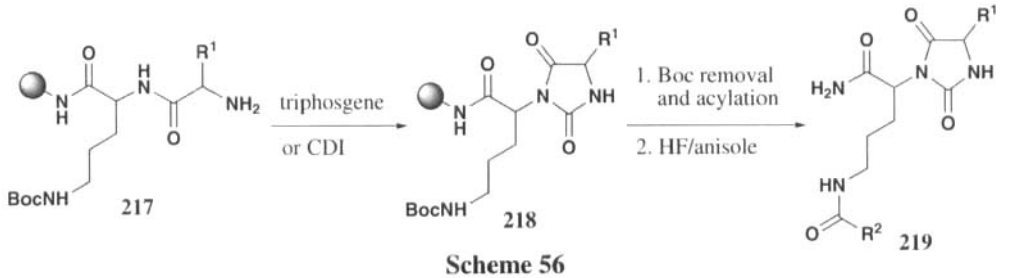


Scheme 55

b) Separate Cyclization and Cleavage Steps

i) Cyclizations Induced by Carbonyldiimidazole or Phosgene Derivatives

Nefzi *et al.* introduced another type of cyclization to solid phase hydantoin synthesis. Primary or secondary amine functionalities of amino acids were treated with carbonyldiimidazole[149] (thiocarbonyldiimidazole)[150] or triphosgene (thiophosgene)[151] to form intermediate isocyanates (isothiocyanates) which underwent a ring closure reaction to yield the corresponding hydantoins (thiohydantoins). Cleavage of the obtained di- or trisubstituted hydantoins **219** resulted from treatment of the resin with HF/anisole in a separate step (*Scheme 56*).



Scheme 56

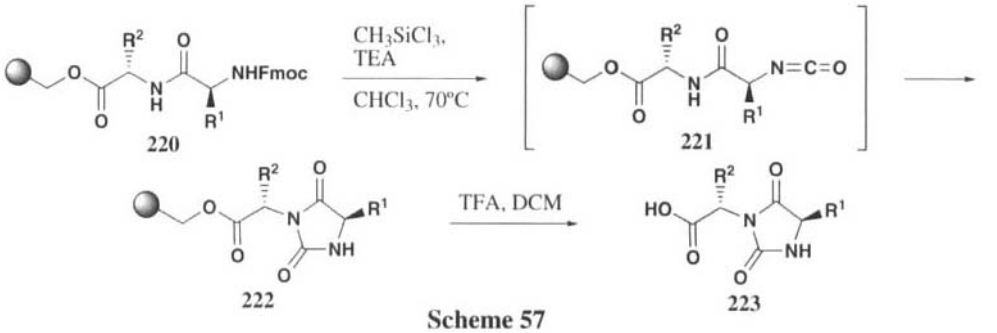
Instead of triphosgene, Bhalay and coworkers applied diphosgene in solid-phase hydantoin synthesis.[152] A further methodology to form more complex structures on solid support was represented in a synthesis of branched thiohydantoin benzimidazolinethiones and thiohydantoin tetrahydroquinoxalinediones.[150]

ii) Other Separate Cyclization and Cleavage Steps

Attaching aldehydes to solid support, *e.g.* a 5-hydroxymethylfurfural template[153] or tetrazolyl biphenyl aldehydes,[20] and reacting them stepwise with an amino acid, $NaBH_3CN$ and an isocyanate led to the formation of the hydantoin ring after treatment with a base. In both reports, release from the resins was performed with TFA.

Heine *et al.* introduced a spot hydantoin synthesis on cellulose membranes.[154] Thereby, an acid treatment led to the cyclization of ureas to hydantoins. Depending on the linker type chosen, simultaneous cleavage occurred or release from a photo-linker was achieved by irradiation.

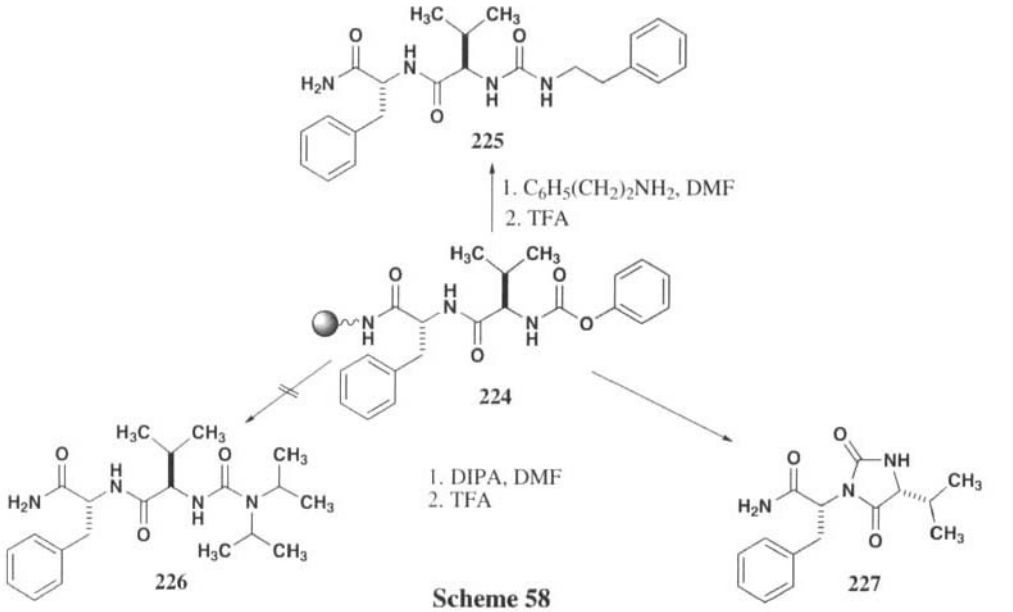
A two-step synthesis starting from Fmoc-protected resin-bound dipeptides **220** was described (*Scheme 57*).[155] Carbamates **220** were converted to the isocyanate intermediates **221**



Scheme 57

by treatment with CH_3SiCl_3 and triethylamine. Mild heating completed the cyclization reaction and, upon acid cleavage, hydantoins **223** were obtained in good purities.

Resin-bound phenyl carbamate dipeptides **224** were treated with primary or secondary amines (*Scheme 58*).[156] On the one hand, with 2-phenylethylamine, an intermolecular reaction to the urea **225** occurred, whereas in the presence of diisopropylamine, intramolecular ring closure to hydantoin **227** was preferred to urea formation. The generated hydantoin was still attached to the resin and had to be cleaved in a separate step.

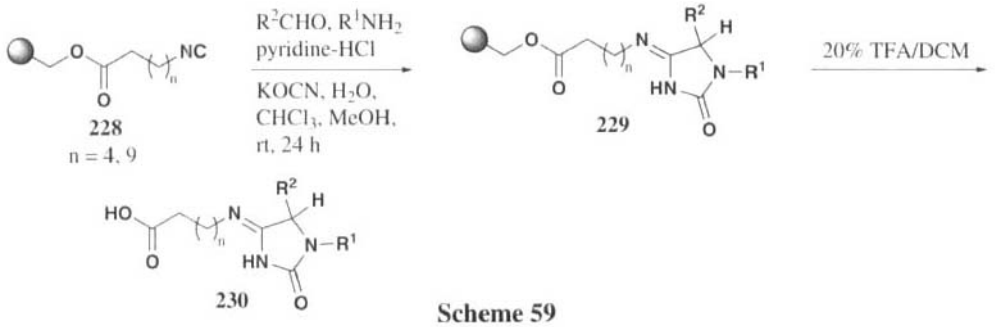


Scheme 58

The terminal amino function of resin-bound peptides could be activated with *N,N'*-disuccinimidyl carbonate to produce succinimidyl carbamates, followed by basic cyclization to hydantoins and detachment from the support.[157] This methodology was used to synthesize rigidified RGD mimetics.

Disubstituted ureas were generated by reacting carboxy-linked phenylalanine on polystyrene resin with *p*-nitrophenyl chloroformate and amino acid methyl esters. Attack of one urea nitrogen to the methyl ester carbonyl led to hydantoin formation, and subsequent cleavage was performed with TFA.[158]

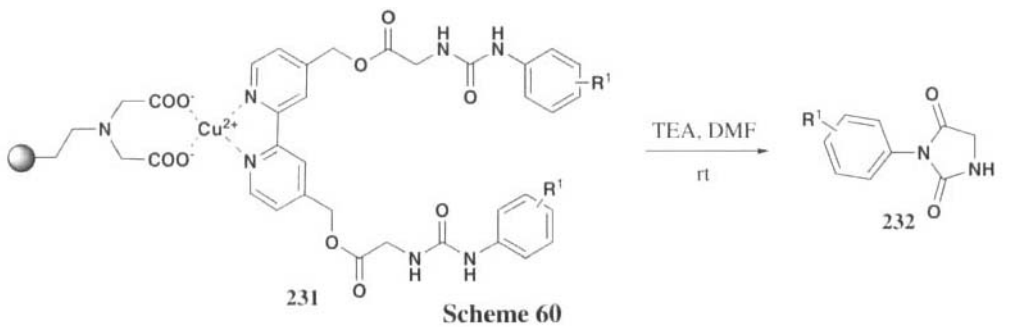
4-Iminohydantoins **230** were synthesized on solid support *via* an Ugi four-component reaction from immobilized isocyanides **228**, aldehydes, primary amines and *in situ*-generated HOCN, followed by acidic cleavage (*Scheme 59*).[159]



Scheme 59

3. Polymer-Bound Reagents in the Synthesis of Hydantoins

The application of polymer-bound reagents can show significant advantages over a normal solution-phase synthesis for they may immobilize intermediates thus allowing for more complete and cleaner reactions. Such methods should not be termed as solid-phase synthesis of hydantoins in a narrow sense, but as hydantoin synthesis supported by polymer-bound reagents. One interesting example was given by Ley and coworkers who attached an amino acid to a 2,2'-bipyridine, treated it with isocyanates and released the hydantoins **232** by cycloelimination (*Scheme 60*).[78] The different intermediates were immobilized *via* the bipyridine-tag and a polymer-bound imino diacetic acid containing complex-bound copper (II) ions.

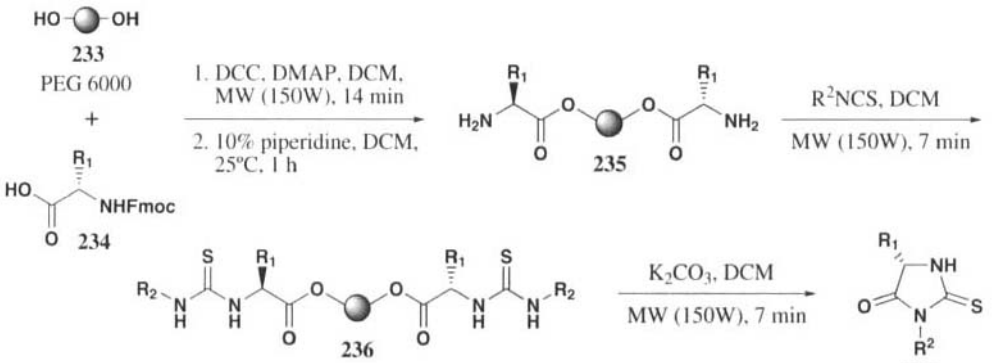


Scheme 60

4. Liquid-phase Organic Syntheses

The International Union of Pure and Applied Chemistry (IUPAC) defined "Liquid Phase Chemistry" as a synthetic process employing a macromolecular *soluble* support[160] to illustrate the differences to solution and solid phase chemistry, working without any polymeric supports or with insoluble macromolecular resins, respectively.

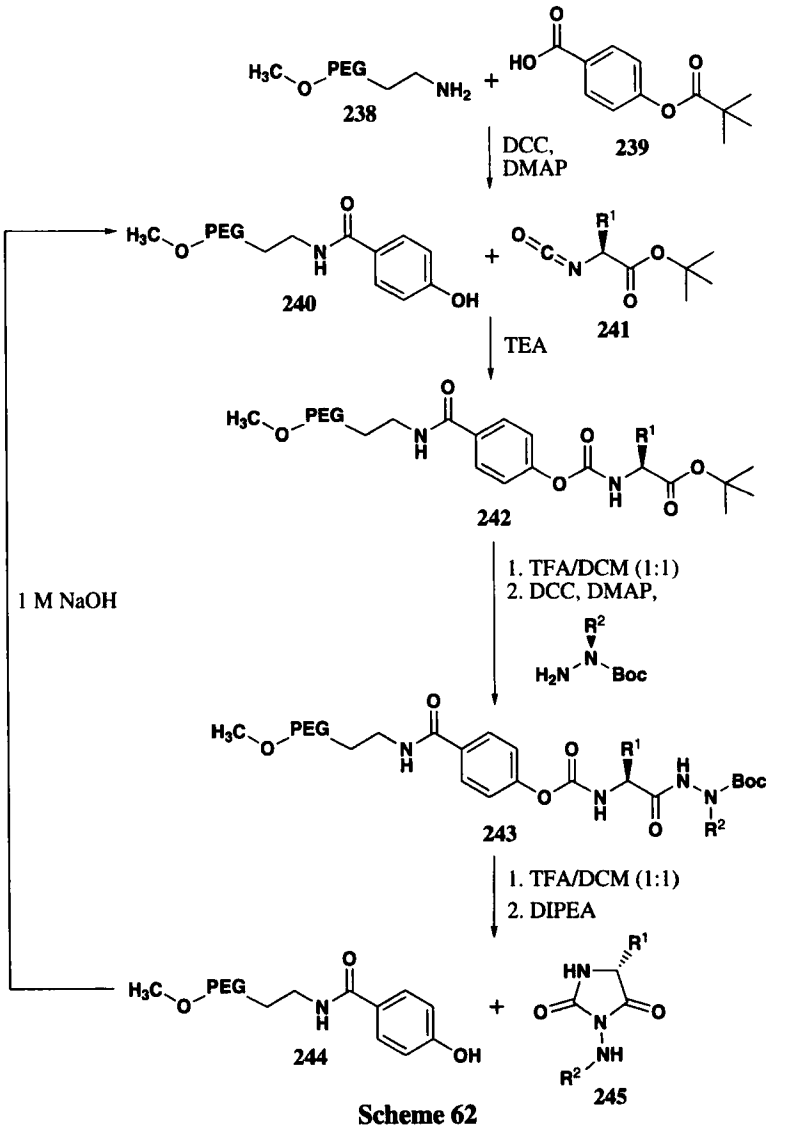
Combination of such a liquid-phase synthesis of (thio)hydantoins with microwave approaches to enhance and accelerate the reactions using PEG 6000 as soluble support has been demonstrated in a few publications.[161] A recent approach is shown in *Scheme 61*.



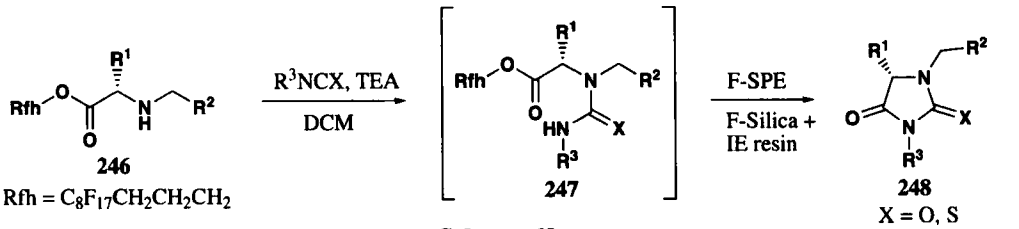
Scheme 61

Yoon and coworkers[162] provided a liquid-phase access to 3-aminohydantoins (*Scheme 62*). To obtain compounds **245**, an isocyanate of a *tert*-butyl amino acid **241** was attached to the polyethylene glycol monomethyl ether (MeO-PEG) polymer **240**. The *tert*-butyl ester was cleaved and a Boc-protected aza-amino acid was coupled using DCC and DMAP. After removal of the Boc group, cyclization and release occurred under basic conditions.

Fluorous synthesis is a complementary type of liquid-phase synthesis that has the character of solution-phase reactivity and a solid-phase type of separation.[191] Zhang and Lu introduced this method to the synthesis of (thio)hydantoins.[163] A perfluoroalkylchain-tag facilitated the compound separation and purification *via* solid-phase extraction (SPE) or HPLC over Fluoro*Flash* silica gel (*Scheme 63*).



Scheme 62

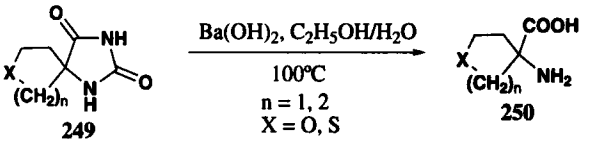


Scheme 63

II. REACTIVITY OF HYDANTOINS AND THEIR DERIVATIVES

1. Hydrolyses of Hydantoins

Hydrolysis of hydantoins can be performed either in an acidic or basic medium. Thus, C-5 substituted hydantoin derivatives are of synthetic utility as precursors to α-amino acids. The hydrolytic degradation proceeds through the intermediacy of ureido acids. On the one hand, this can be accomplished by biocatalytic conversion, *e.g.* using microbial or plant hydantoinases to produce ureido acids. The further transformation to amino acids can then be catalyzed by other enzymes or acids.[164] However, detailed aspects of this valuable method to obtain optically pure *D*- and *L*-amino acids are not reviewed herein. On the other hand, the formation of amino acids from hydantoins can be achieved non-enzymatically. In this manner, rare, unnatural amino acids can be prepared from easy to produce hydantoins both under acidic or basic conditions. Exemplarily, Tellier and coworkers[56] took advantage of this behaviour of hydantoins to generate aminobicyclo[2.2.1.]heptane dicarboxylic acids from spirohydantoins by acidic hydrolysis. Heating with aqueous alkali was frequently applied in the hydrolysis of non-racemizable 5,5-disubstituted hydantoins.[57,59,60] An example is given in *Scheme 64*.[58]



Scheme 64

Kinetic investigations on the cleavage and cyclization of hydantoins and ureido acids, respectively, were described by Kaválek *et al.*[165] and Blagoeva *et al.*[166]

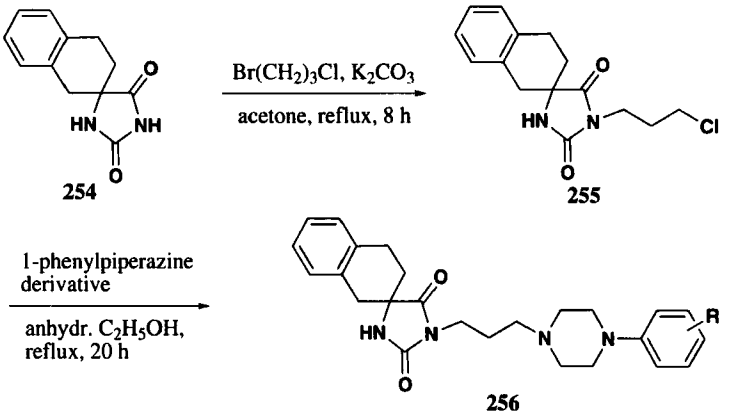
2. *N*-Alkylations with Electrophilic Reagents

N-unsubstituted hydantoins can easily be monoalkylated at the imide nitrogen in position 3, whereas substitution of both nitrogens in one step requires much harder conditions. Alkylation at amide N-1 could be done after first protecting the N-3.[1,11c,13,167] However, reaction at N-1 was favoured in case of an intramolecular attack to give a tetracyclic hydantoin derivative.[51] N-3 alkylation of hydantoins is a commonly applied reaction to modify the core scaffold and thereby the properties of the resulting substances.[168] Water soluble prodrugs of phenytoin were also designed by attaching suitable side chains to position 3.[2f,2h] Typically, an alkaline hydantoin solution is treated with alkyl halides[18b,169] sometimes employing a phase-transfer catalyst[10d,11c,61] or silylated hydantoins.[10c] The cystine derived hydantoin **251** was treated with excess benzyl bromide to give the desired 5-methylene hydantoin **252** (*Scheme 65*).[69]

251 252 253

Scheme 65

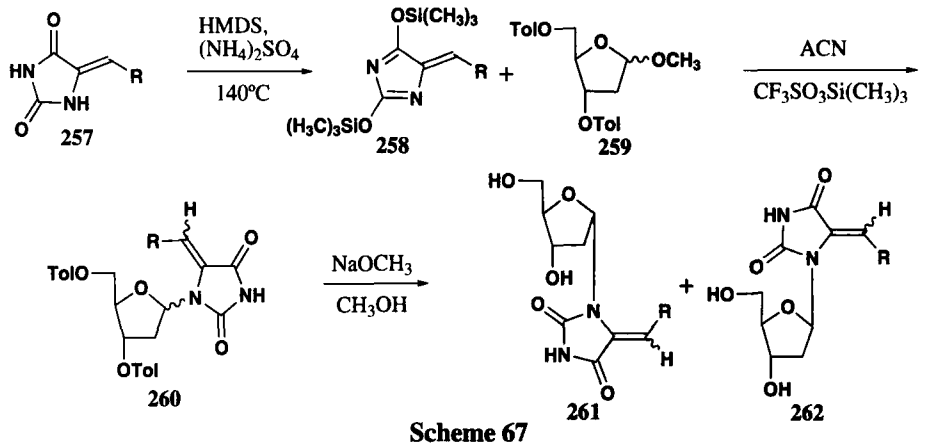
When dihaloalkanes such as dibromoalkanes or bromochloroalkanes were used, the resulting alkylated hydantoins could be treated with amines (*e.g.*, *Scheme 66*[3e]) or potassium thioacetate to obtain hydantoins with a basic side-chain[3a,11b,170] or hydantoin ethanethiol derivatives, respectively.[167]



254 255 256

Scheme 66

A synthetic route to the matrix metalloproteinase inhibitor Trocade® (Ro 32-3555) included bromomethylation of 1,5,5-trimethylhydantoin. The resulting 3-bromomethyl compound was used to alkylate a malonic ester derivative.[7a] Cyanohydantoins were prepared by reaction of the parent hydantoins with a cyanogen halide and a base. The cyano group was attached either at the N-3 or at both nitrogens.[171] Among the modifications at the N-1 nitrogen, the preparations of hydantoin nucleosides were prominent examples.[21b,172] Thereby, *O*-silylated hydantoins **258** were attached to protected 2-deoxy-D-ribofuranoside **259** granting the desired thymidine analogues **260** (*Scheme 67*).[172]

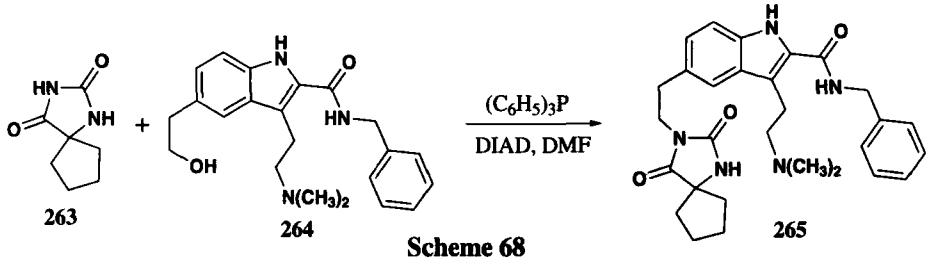


Scheme 67

An example for the reaction of the 2-thiohydantoin sulfur with electrophiles was the *S*-glucosylation with glycosyl halides under alkaline conditions.[21c]

3. *N*-Alkylations by Mitsunobu Coupling

The Mitsunobu reaction comprises the condensation of an alcohol and a nucleophile using the redox couple of a trialkyl or triaryl phosphine and a dialkyl azodicarboxylate. For instance, 4-nitrophenethyl alcohol[3c] or the 5-ethyl alcohol tryptamine derivative **264** (*Scheme 68*)[3d] were

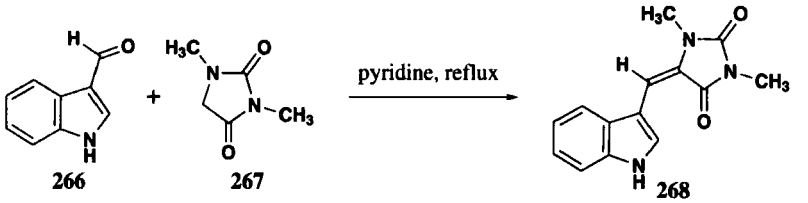


Scheme 68

reacted under Mitsunobu conditions with hydantoin or the spirohydantoin **263**, respectively. Further examples for Mitsunobu couplings were given by Alcaraz *et al.*[12] in the synthesis of novel $P2X_7$ receptor antagonists and by Raja in the synthesis of a [^{14}C] labelled matrix metalloproteinase inhibitor.[7b]

4. Aldol-type Reactions

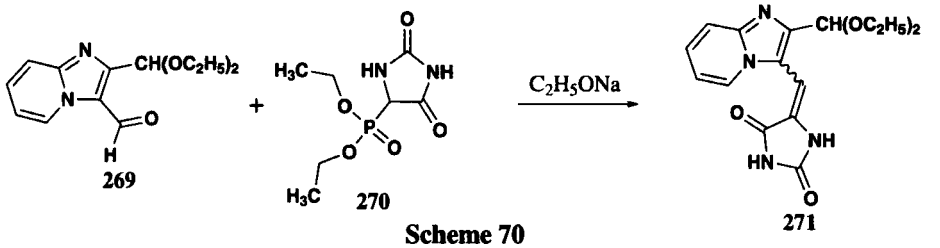
Hydantoins having a free methylene group in the C-5 position can be condensed with aldehydes resulting in C-5-unsaturated compounds. Examples for this reaction already have been summarized by Lopez and Trigo.[1] Several novel works have been published[21,173] including the synthesis of the aplysinopsin derivative **268** (*Scheme 69*)[5a] and hydantocidin[33], natural compounds containing a hydantoin moiety. Adding enantiopure aldehydo sugars to *N*-protected hydantoin, 5-(alditol-1-*C*-yl)-hydantoin could be obtained.[174]



Scheme 69

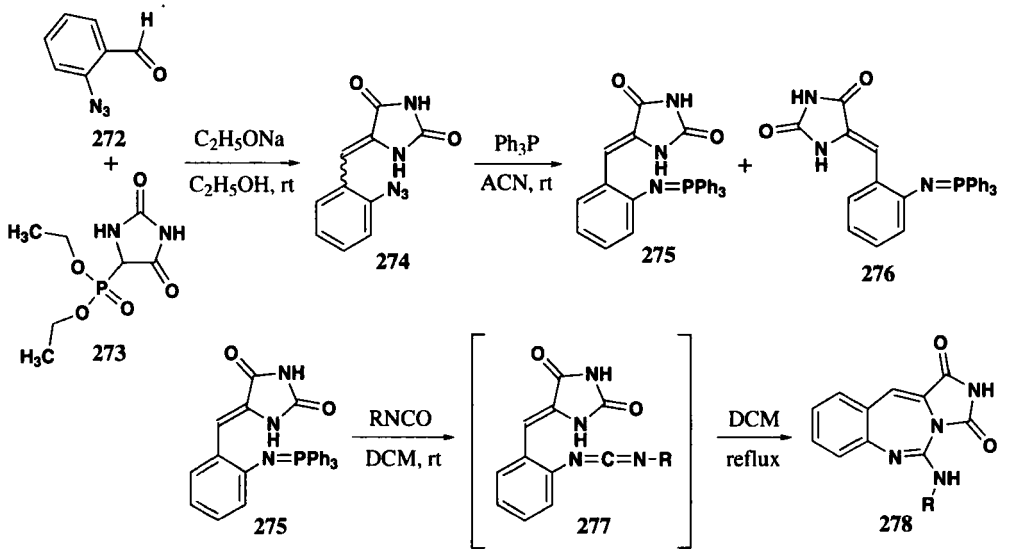
5. Horner-Wadsworth-Emmons Reactions

The Horner-Wadsworth-Emmons reaction encompasses the reaction of phosphonic acid dialkylesters with carbonyl compounds. Thus, starting from diethyl 2,4-imidazolidinedione-5-phosphonate **270**[175] and the aldehyde **269**, the C-5 unsaturated hydantoin **271** could be obtained (*Scheme 70*).[176]



Scheme 70

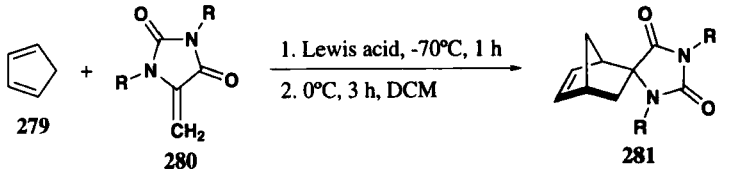
Further examples illustrated the usage of this synthetic route in annulation reactions yielding dichloroimidazo[4,5-*b*]quinolin-2-one[177] and imidazo[1,5-*c*][1,3]benzodiazepines **278** (*Scheme 71*).[178]



Scheme 71

6. Cycloaddition Reactions of Hydantoins

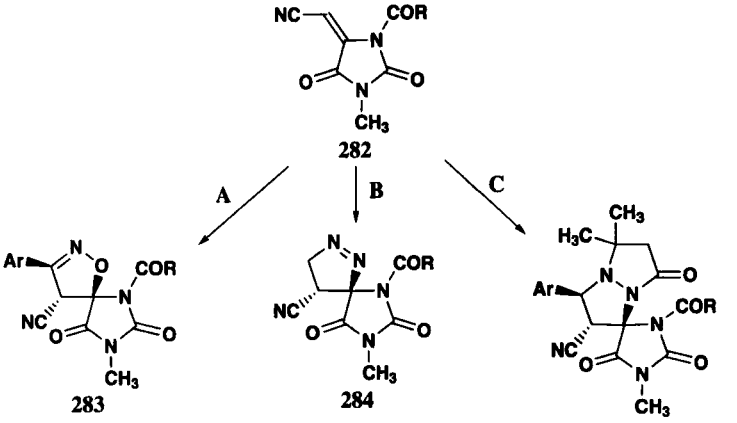
Sankhavasi and coworkers reported a Diels-Alder reaction of a 5-methylene hydantoin **280** (R = (*S*)-1-phenylethyl) acting as dienophile with cyclopentadiene acting as diene (*Scheme 72*).[179]



279 280 281

Scheme 72

A number of 1,3-dipolar cycloadditions were performed starting from hydantoins **282** (*Scheme 73*) using 2,4,6-trimethoxybenzonitrile *N*-oxide (**A**), diazomethane (**B**), and (1*Z*)-5,5-dimethyl-3-oxo-1-[(2,4,6-trimethoxyphenyl)methylidene]pyrazolidin-1-ium-2-ide (**C**) as 1,3-dipoles, respectively.[180]



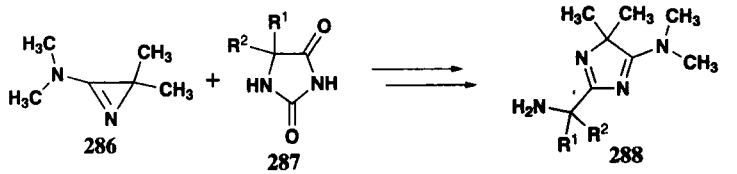
282 283 284 285

R = CH_3, C_6H_5
Ar = 2,4,6-trimethoxyphenyl

Scheme 73

7. Other Reactions of Hydantoins

5,5-Disubstituted hydantoins **287** have been shown to react with 3-(dimethylamino)-2,2-dimethyl-2*H*-azirine **286** to give 4*H*-imidazoles **288** in a very complex ring transformation reaction (*Scheme 74*).[181] 1,3-Dibromo-5,5-dimethylhydantoin (DBH) can be used as a stable and easy to handle brominating agent.[182]



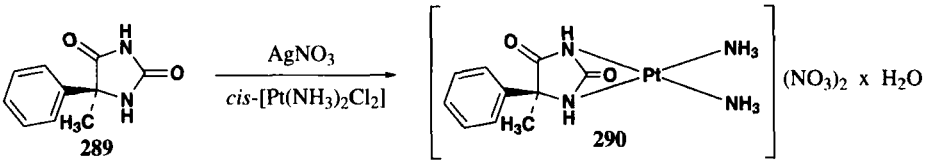
286 287 288

Scheme 74

8. Complexation of Hydantoins with Metal Ions

Interactions of hydantoins with metal ions, such as copper(II) (Zwikker test) or cobalt(II) (Parri test) are widely used in colour reactions for identification.

Because complexes of the transition metal platinum constitute well-established antineoplastic drugs, such as cisplatin or carboplatin, five-membered heterocyclic ligands containing two or more nitrogens, *e.g.* hydantoins, have sparked a great deal of interest.[183] Platinum(II) complexes *e.g.* with 5-methyl-5-phenylhydantoin **289** (*Scheme 75*) have been synthesized and found to be effective in cytotoxicity tests.[184]



289 290

Scheme 75

Among other transition metal complexes with hydantoin ligands iron(II)[185], nickel(II)[186], copper(II)[187] and gold(I)[188] complexes have been synthesized and characterized. Moreover, the complexations of 5,5-diphenylhydantoin or hydantoin itself with silver(I)-, zinc(II)-, and cadmium(II) ions[189] or with antimony(V) and mercuric(II) ions[190] have been described.

Acknowlegement.- The authors thank the DFG Graduiertenkolleg 804 "Analyse von Zellfunktionen durch kombinatorische Chemie und Biochemie" for financial support. Many thanks to Reik Löser for reading the proof and for useful advice.

ABBREVIATIONS

Ac = acetyl

ACC = *N*-acetylcysteine

ACN = acetonitrile

ANRORC = addition of a nucleophile, ring opening, ring closure

Ar = aryl

Boc = *tert*-butyloxycarbonyl

BSA = *N,O-bis*(trimethylsilyl)acetamide

BSTFA = *N,O-bis*(trimethylsilyl)trifluoroacetamide

CB 1 = cannabinoid 1 (receptor)

CDI = carbonyldiimidazole

CSI = chlorosulfonyl isocyanate

DBU = 1,8-diazabicylco[5.4.0]undec-7-ene

DCC = dicyclohexyl carbodiimide

DCE = dichloroethane

DCM = dichloromethane
DIAD = diisopropyl azodicarboxylate
DIC = diisopropyl carbodiimide
DIPA = diisopropylamine
DIPEA = diisopropylethylamine
DMA = *N*,*N*-dimethylacetamide
DMAD = dimethyl acetylenedicarboxylate
DMAP = 4-dimethylaminopyridine
DMF = dimethylformamide
DMSO = dimethyl sulfoxide
DNA = desoxyribonucleic acid
DPT = di-2-pyridylthiocarbonate
FDA = Food and Drug Administration
Fmoc = 9-Fluorenylmethyloxycarbonyl
HDL = high density lipoprotein
HLE = human leukocyte elastase
HMDS = hexamethyldisilazane
HOBt = hydroxy benzotriazole
5-HT = 5-hydroxytryptamine
HTS = high throughput screening
Im = imidazole
LFA-1 = lymphocyte function-associated antigen-1
MW = microwave(s)
Ms = mesyl
NMDA = *N*-methyl-D-aspartate
NMR = nuclear magnetic resonance
PDE 5 = phosphodiesterase 5
PEG = polyethylene glycol
PET = positron emission tomography
P-gp = P-glycoprotein
PhSH = thiophenol
PPE = polyphosphoric ester
rt = room temperature
SPC = summary of product characteristics
SPE = solid-phase extraction
SPOS = solid-phase organic synthesis
SPPS = solid-phase peptide synthesis
TBDM = tetrabutyldimethyl

TFA = trifluoroacetic acid

THF = tetrahydrofuran

TMAD = tetramethylazodicarboxamide

TMEDA = *N,N,N',N'*-tetramethyl-1,2-ethanediamine

Tol = toluyl

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